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BY

DR H. LANDOLT

PROFESSOR OF CHEMISTRY IN THE UNIVERSITY OF BERLIN

TRANSLATED WITH THE AUTHOR'S PERMISSION

BY

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PREFACE

This forms the eighth chapter of the first volume of Graham-Otto's 'Lehrbuch der Chemie.' Fuller details on the subject can be found in Dr. Landolt's 'Das optische Drehungsvermögen organischer Substanzen und dessen praktische Anwendungen,' 1898, of which this is an extract with the addition of results published since the middle of 1897.

Notes and additions inserted by the translator are enclosed in square brackets [ ].

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Lieb. Ann.	*Liebig's Annalen der Chemie.*
Ann. chim. phys.	*Annales de Chimie et de Physique.*
Ber.	*Berichte der deutschen chemischen Gesellschaft.*
Bull.	*Bulletin de la Société chimique de Paris.*
C. r.	*Comptes rendus de l'Académie des Sciences.*
J. C. S.	*Journal of the Chemical Society.*
Zt. ph. Chem.	*Zeitschrift für physikalische Chemie.*

In all references to journals the date of publication is given in brackets ( ).

Addendum to pages 121–131. *Isomeric Compounds.*

In connection with the effect of the introduction of the toluyl radicle into an active acid, it is worthy of note that the isomeric phenâcetyl group exerts a very different influence. In fact, the influence of this latter is essentially similar to that of the acetyl group, which points to the conclusion that the rotatory effect of a group depends upon its distance from the asymmetric carbon atom. This conclusion was first arrived at by Frankland (*J. C. S.* **63** (1893), 535), and was later confirmed by Frankland and MacGregor (*J. C. S.* **69** (1896), 119), by Freundler (*Ann. chim. phys.* [7], **3** (1894), 433), and by Tchugaeff (*Ber.* **31** (1898), 306, 1778).

Methyl glycerate	$[\alpha]^{20}_{D}$ = − 4·80	$[M]^{20}_{D}$ = − 5·76
,, di-*o*-toluyl glycerate	,, = + 20·2	,, = + 71·91
,, ,, *m* ,, ,,	,, = + 26·4	,, = + 93·98
,, ,, *p* ,, ,,	,, = + 41·2	,, = + 146·67
,, diphenacetyl ,,	,, = − 15·84	,, = − 56·50
,, diacetyl ,,	$[\alpha]^{15}_{D}$ = − 12·04	$[M]^{15}_{D}$ = − 24·56

Frankland and MacGregor } See page 127.
Frankland and Aston

Diethyl tartrate	$[\alpha]^{20}_{D}$ = + 7·66	$[M]^{20}_{D}$ = + 15·8
,, di-*o*-toluyl tartrate	[1] $[\alpha]^{100}_{D}$ = − 54·7	$[M]^{100}_{D}$ = − 241·9
,, di-*m* ,, ,,	,, = − 63·7	,, = − 281·7
,, di-*p* ,, ,,	,, = − 90·0	,, = − 397.7
,, diphenacetyl ,,	[2] $[\alpha]_{D}$ = + 20·2	$[M]_{D}$ = + 89·3
,, diacetyl ,,	[3] $[\alpha]^{17}_{D}$ = + 1·02	$[M]^{17}_{D}$ = + 2·96

[1] Frankland and Wharton, *J. C. S.* **69**, 1309.
[2] Freundler. *l.c.* In alcohol : $c.$ = 0·9077.
[3] Pictet, *Jahresber.* 1882, 856. In alcohol : $c.$ = 23·644.

Menthol	$[\alpha]_{D}$ = − 50·0	$[M]_{D}$ = − 78
Menthyl *o*-toluate	,, = − 84·4	,, = − 231·3
,, *m*- ,,	,, = − 87·9	,, = − 241·0
,, *p*- ,,	,, = − 92·1	,, = − 252·5
,, phenacetate	,, = − 69·6	,, = − 190·7
,, acetate	,, = − 79·4	,, = − 157·3

Tchugaeff, *l.c.*

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OPTICAL ACTIVITY

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1. General Principles of Optical Activity.

1. Introduction.—A number of substances are endowed with the property of being able to rotate through a certain angle the plane of vibration, or the plane of polarisation, of a plane-polarised ray of light which is passed through them. Some of these substances rotate the plane to the right, others rotate it to the left. Such substances are said to be *optically active*, or circular-polarising, and the phenomenon itself is called *optical activity*.

Polarisation-apparatus for the recognition of this behaviour, and for measuring the angle of rotation, are described in treatises on physics and physical chemistry. Here a knowledge of these will be assumed.

We distinguish two types of optical activity, viz. :—

(*a*) When a polarised ray is passed through a plate of a crystal of some few inorganic and organic compounds, the plane of polarisation is rotated. In these cases the cause of the rotatory power is to be found in the structure of the crystal, because the activity is lost when the substance is converted into the amorphous state, either by being fused or dissolved. The action is, therefore, termed *crystal rotation.*

(*b*) A very large number of compounds (all belonging to the class of carbon compounds) are possessed of this rotatory power, both in the liquid and in the dissolved state. This so-called *liquid rotation* occurs also if the substances be examined in the form of normal vapours, and consequently it cannot be caused by molecular grouping, but must be due to the chemical molecule. On this account it is also called *molecular rotation.*

In the following paragraphs those two types of rotation will be more definitely characterised.

2. **Crystal Rotation.**—This is found only in such crystal-polyhedra of the regular, hexagonal and tetragonal systems as possess the property of being able to occur in what is crystallographically known as enantiomorphic forms, *i.e.* in two non-symmetrical forms which cannot be superposed. One of the polyhedra is the mirror-image of the other.

Corresponding to the two enantiomorphic forms, every active crystalline substance appears in the form of dextrorotatory and lævorotatory individual crystals, the action of which for equal lengths through which the polarised light passes is exactly the same in degree but opposite in direction. The different direction which the rotation will have can often be recognised on the geometrical structure of the crystals by the occurrence of so-called hemihedral or tetartohedral faces which are oppositely disposed on the two different kinds. The best-known example of this is quartz.[1]

In the case of every active crystal the observed angle of rotation is proportional to the thickness of the plate examined; the angle is generally specified with reference to a plate 1 mm. thick. The angle of rotation is further dependent on the wave-length of the light used. The yellow light emitted from a sodium flame is usually employed, and the observed angle is denoted by α_D, because it is referred to rays of the wave-length of the Fraunhofer D line.

So far crystal rotation has only been observed for the substances enumerated in the following table. In the table both the crystal system and group (according to Liebisch's method) is given.

REGULAR SYSTEM.

(TETARTOHEDRAL GROUP.)

	α_D for 1 mm.
Sodium chlorate, $NaClO_3$	± 3°·14
Sodium bromate, $NaBrO_3$	2·17
Sodium sulphantimoniate, $Na_3SbS_4 + 9H_2O$	2·37
Sodium uranyl acetate, $Na.UO_2(C_2H_3O_2)_3$	1·48

---

[1] For details on enantiomorphism see Th. Liebisch's *Grundriss der physikalischen Krystallographie*, Leipsic, 1896, and P. Groth's *Physikalische Krystallographie*, 3rd edition, Leipsic, 1895.

HEXAGONAL SYSTEM.

(Trapezohedral-Hemihedral Group.)

	α_D for 1 mm.
*Cinchonine antimonyl tartrate, $C_{19}H_{22}N_2O.SbO.C_4H_4O_6 + 2\frac{1}{2}H_2O$	9·79

(First Hemimorphic-Tetartohedral Group.)

Potassium lithium sulphate, $KLiSO_4$	3·44
Ammonium lithium sulphate, $(NH_4)LiSO_4$	—
Rubidium lithium sulphate, $RbLiSO_4$	—
Potassium sulphate-lithium chromate, $K_2SO_4 + LiCrO_4$	1·93

(Trapezohedral-Tetartohedral Group.)

Quartz, SiO_2	21·723
Cinnabar, HgS (for red light 270 to 300°)	—
Potassium dithionate, $K_2S_2O_6$	8·39
Rubidium dithionate, $Rb_2S_2O_6$	—
Calcium dithionate, $CaS_2O_6 + 4H_2O$ (for green light 2·09°)	—
Strontium dithionate, $SrS_2O_6 + 4H_2O$ (for green light 1·64°)	—
Lead dithionate, $PbS_2O_6 + 4H_2O$	5·53
*Rubidium tartrate, $Rb_2C_4H_4O_6$	10·18
*Cæsium tartrate, $Cs_2C_4H_4O_6$	—
*Japan camphor, $C_{10}H_{16}O$	0·65
*Matico camphor, $C_{12}H_{20}O$	1·92
*Patchouli camphor, $C_{15}H_{26}O$[1]	1·325
Benzil, $C_6H_5.CO.CO.C_6H_5$	24·84

(Ogdohedral Group.)

Sodium periodate, $NaIO_4 + 3H_2O$	23·3

TETRAGONAL SYSTEM.

(Trapezohedral-Hemihedral Group.)

Ethylene diamine sulphate, $(N_2H_4.C_2H_4)H_2SO_4$	15·5
Guanidine carbonate, $(CH_5N_3)H_2CO_3$	14·58
Diacetyl phenolphthaleïn, $C_{20}H_{12}(C_2H_3O_2)_2O_4$	19·7
Sulphobenzene trisulphide, $(C_6H_5.SO_2.S)_2S$	—
Sulphotoluene trisulphide $(C_7H_7.SO_2.S)_2S$	—
*Strychnine sulphate, $(C_{21}H_{22}N_2O_2)_2H_2SO_4 + 6H_2O$	13·25
*Zinc bimalate, $Zn(C_4H_5O_5)_2 + 2H_2O$	3·02

---

[1] Probably belongs to this group.

The regular crystals which are active show a rotation of the plane of polarisation in every direction; those which belong to the hexagonal or tetragonal systems only in the direction of the optical axis.

The substances denoted by an asterisk (*) also possess the power of rotating the plane of polarisation in solution; in these cases the single molecules must be also endowed with optical rotatory power. For them the rotation produced by the crystal is the sum of the effects due to the crystalline structure and to the molecule. Thus it has been proved that for Matico camphor the circular-polarisation effect of the crystal is $\frac{5}{6}$ crystal rotation and $\frac{1}{6}$ molecular (or liquid) rotation.[1]

Active crystals retain their rotatory power when converted into fine powder; and the degree of rotation is not diminished. This can be observed with sodium chlorate by suspending the powder in an inactive liquid whose index of refraction is equal to that of the solid, for which purpose a mixture of alcohol and carbon disulphide may be used. When correct proportions of these have been chosen the crystal-powder becomes invisible, and the liquid is put into a polarimeter-tube, which must be rotated on its axis so as to keep the powder in suspension.

3. Liquid Rotation. Molecular Rotation.—This occurs only with organic substances. Some of these are natural products or their derivatives, and some have been synthetically prepared. We are now acquainted with over 700 active carbon compounds, which belong to the following groups:—

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[1] For details see Landolt, *Optisches Drehungsvermögen*, 2nd edition, 1898, pages 12 to 16.

1. Hydrocarbons:
    Methyl-ethyl-propyl-methane, diamyl, &c.
2. Alcohols with 1 atom of oxygen:
    Methyl-ethyl-carbinol, amyl alcohol and its derivatives, hexyl alcohols.
3. Alcohols with 2 atoms of oxygen:
    Propylene glycol and its derivatives, diphenyl glycol.
4. Alcohols with 5 atoms of oxygen:
    Arabitol, rhamnitol, quercitol.
5. Alcohols with 6 atoms of oxygen:
    Mannitol, sorbitol, iditol, rhamnohexitol, inositol.
6. Alcohols with 7, 8, and 9 atoms of oxygen:
    Volemitol, glucoheptitol, mannoheptitol, glucooctitol, mannooctitol, glucononitol.
7. Acids with 2 atoms of oxygen and their derivatives:
    Valeric acid, caproic acid.
8. Acids with 3 atoms of oxygen and their derivatives:
    Ethylidene lactic acid, oxybutyric acid, phenylglycollic (mandelic) acid, tropic acid, parasorbic acid, &c., alanine, leucine, cystine, tyrosine.

9. Acids with 4 atoms of oxygen and their derivatives:

Pyrotartaric acid, glyceric acid, phenyl-α-bromolactic acid, phenyl-dibromopropionic acid, &c.

10. Acids with 5 atoms of oxygen and their derivatives:

Trioxybutyric acid, malic acid and its derivatives, chlorosuccinic acid, methoxysuccinic acid, aspartic acid, asparagine, oxyglutaric acid, glutaminic acid, shikimic acid.

11. Acids with 6 atoms of oxygen and their derivatives:

Tartaric acid, arabonic acid, ribonic acid, rhamnonic acid, xylonic acid, saccharinic acid, quinic acid.

12. Acids with 7 atoms of oxygen and their derivatives:

Trioxyglutaric acid, saccaronic acid, gluconic acid, gulonic acid, mannonic acid, idonic acid, galactonic acid, talonic acid, rhamnohexonic acid.

13. Acids with 8 atoms of oxygen and their derivatives:

Saccharic acid, isosaccharic acid, mannosaccharic acid, idosaccharic acid, talomucic acid, glucoheptonic acids, mannoheptonic acid, &c.

14. Acids with 9 and 10 atoms of oxygen and their derivatives:

Glucooctonic acids, mannooctonic acids,

pentoxypimelic acids, glucononomic acid, mannononomic acid.

15. Oxyaldehydes, aldoses:
    - Pentoses: Arabinose, rhamnose, fucose, xylose, lyxose.
    - Hexoses: Glucose, gulose, mannose, galactose, talose, sorbose, idose, rhamnohexose.
    - Heptoses: Glucoheptose, mannoheptose, rhamnoheptose.
    - Octoses: Glucooctose, mannooctose.
    - Nonoses: Gluconononose, mannonononose.
16. Oxyketones, ketoses:
    - Fructose.—Invert sugar.
17. Disaccharides:
    - Cane sugar, milk sugar, maltose, trehalose (=mycose), &c.
18. Tri- and polysaccharides:
    - Meletriose, melezitose, gentianose, lactosin, &c.
19. Carbohydrates $(C_6H_{10}O_5)_n$:
    - Starch, dextrin, glycogen, inulin, irisin, &c.
20. Gum resins:
    - Arabin, wood-gum, &c.
21. Pectic substances.
22. Terpenes and camphors:
    - A. Aliphatic terpenes—
        - Licarene, licareol, rhodinol (geraniol), citronellal, &c.

- B. Terpane group :
  - 1. Hydrocarbons : Limonene, sylvestrene, phellandrene.
  - 2. Alcohols : Menthol, terpineol, isopulegol.
  - 3. Amine-bases : Menthylamine.
  - 4. Ketones : Menthone, pulegone, carvone.
- C. Camphane group :
  - 1. Hydrocarbons : Camphene, pinene, isoterpene.
  - 2. Alcohols : Borneol, fenchyl alcohol, camphenol, &c.
  - 3. Amines : Bornylamine, fenchylamine.
  - 4. Ketones : Camphor and its derivatives, fenchone, carone, &c.
- D. Polyterpenes :
  - Sesquiterpenes, diterpenes, triterpenes.

23. Ethereal oils :
    - Oil of bergamot, turpentine oil, caraway oil, oil of lavender, &c.
24. Resin acids :
    - Dextropimaric acid, sylvic acid, podocarpic acid, &c.
25. Alkaloids :
    - A. Liquid alkaloids—
      - Methyl-piperidine, ethyl-piperidine, propyl-piperidine (conine), nicotine.

B. Solid alkaloids—
  1. Cinchona group: Quinine, cinchonine, quinidine (conchinine), &c.
  2. Opium group: Morphine, codeïne, narcotine, &c.
  3. Strychnine group: Strychnine, brucine.
  4. Aconite group: Aconitine, atropine, hyoscyamine, &c.
  5. Other alkaloids: Pilocarpine, colchicine, hydrastine, &c.

26. Glucosides:

Amygdalin, coniferin, helicin, salicin, populin, &c., artificial glucosides.

27. Bitter principles, indifferent substances, dyestuffs:

Santonin group: santonin, santonic acid, santoic acid, &c.

Echicerin, quassin, picrotoxin, hæmatoxylin, &c.

28. Bile constituents:

Cholesterine, glycocholic acid, cholalic acid, &c.

29. Albuminoids:

α-glutin, β-glutin, chondrin.

30. Proteïn substances:

Albumen, albumoses, fibrogen, globulin, crystallin, syntonin, albuminates, caseïn.

We know most of these active carbon compounds in two isomeric forms, one of which turns the plane of polarisation to the left, through exactly the same angle as the other, under similar conditions (length of layer, concentration of solution, &c.), turns it to the right. These two forms are termed the antipodes of the substance, and the right-rotating form is denoted by + or *d* (dextrogyrate), whilst the left-rotating form is denoted by − or *l* (lævogyrate).

When an organic *d*- compound takes part in a chemical reaction, the product may be either dextrorotatory or lævorotatory. In order to indicate the derivation, all the substances belonging to a group derived from one *d*- substance are denoted by *d*-, without in any way indicating by this that the substance is actually dextrorotatory. If it is desired to state the rotation of the derived compound, this may be done by adding + or −, so that the signs *d* (+) and *d* (−) denote dextro- and lævorotatory substances obtained from a dextro-compound, and *l* (+) and *l* (−) are applied to the dextro- and lævorotatory derivatives of a lævo- compound.

Those active carbon compounds which are present in animal and plant cells occur as a rule only in one of the active forms, and the other is unknown. This is the case for the di- and poly-saccharides, carbohydrates $(C_6H_{10}O_5)_n$, alkaloids, bitter principles, glucosides, bile constituents, and proteïns. In the case of some of the terpenes and camphors, both antipodes have been found in Nature, but not in the same plant. Thus, *d*- and *l*-pinenes have been discovered in different species of *Pinus*.

If equal weights (and, consequently, an equal number of molecules) of the two antipodes of a crystallisable substance be mixed in solution, then the crystals which separate out are devoid of rotatory power. The crystals thus obtained may, by certain means, be again split up into the active components. Inactive substances of this type are termed *racemic* compounds, because the principal representative of the type is racemic acid, which consists of *d*- and *l*-tartaric acids. To denote this form of isomer, the letter r (or also $d\,l$ or $d+l$) is in general use.

Racemic compounds are invariably formed when an attempt is made to synthetically prepare an active substance, equal quantities of the *d*- and of the *l*- compound being produced in the chemical reaction.

For certain substances, besides the racemic form, a second inactive modification may be obtained. This modification is characterised by resisting all attempts to decompose it into active antipodes. This occurs in the case of compounds, whose molecule consists of two similar atom-groups; and the inactivity is explained by the two half-molecules being possessed of equal but opposite activities. Those so-called *constitutionally-inactive* modifications are denoted by i. The principal representative of the class is meso-tartaric acid.

Substances of certain atomic constitution may, as will be pointed out in Section 12, form several pairs of active antipodes, and consequently several *r*- modifications, and, under certain circumstances, also several *i*- forms.

4. Measurement of Rotation. Specific Rotation.—As Biot[1] at the beginning of the century showed, the size of the angle of rotation which an active liquid causes in the polarisation apparatus is dependent on the following circumstances:

(*a*) On the length of layer through which the light passes, the angle being directly proportional to this length. As unit of length in the case of liquids, one decimetre is usually adopted.

(*b*) On the wave-length of the light ray used. Just as the refraction of ordinary light increases with decrease of wave-length, so also does the rotation of polarised light. The rotation is smallest for the red and greatest for the violet rays.

As in the examination of active crystals (Section 2), so also for liquids the yellow light from a sodium flame is generally used.

If the angle of rotation be determined for a number of light rays of known wave-length, we obtain the rotation-dispersion of the substance. This may have a normal course, as is the case for cane sugar solution, turpentine, &c. Certain liquids, however, such as aqueous solutions of malic and tartaric[2] acids, do not rotate the plane of polarisation to a regularly increasing extent as the refraction of the ray increases (or as the wave-length decreases); but for some colour lying between red and violet a maximum or a minimum is reached. It may also happen that at certain concentrations the angle of rotation at first diminishes with decreasing wave-length, and for certain rays becomes zero; then, as the wave-length further decreases, the rotation increases, but in the opposite direction—*i.e.* a reversion of the direction of rotation takes place. Such phenomena are termed anomalous rotation-dispersions.[1]

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[1] Biot, *Mém. de l'Acad.* **2**, 41, 91 (1817).

[2] [On the anomalous rotation-dispersion of tartaric acid see Wendell, *Wied. Ann.* **66**, 1149 (1899); Lepeschkin, *Ber.* **32**, 118 (1899)

(*c*) On the temperature. If the angle of rotation of a liquid be determined at increasing temperatures, taking into account in the calculation that the length of the tube increases (by 0·0000085 per degree, if it is made of glass), it is generally found that the angle calculated for equal lengths diminishes. This may be due to the diminution of the density or the increase in the volume of the liquid which takes place, whereby the light is caused to pass through a smaller number of active particles. If this be the only factor conditioning the change in the rotation, then when the observed angle is divided by the density of the liquid at the same temperature the quotient should remain constant; but, instead, we find that this quotient either increases (nicotine, the esters of *l*-glyceric acid, tartaric acid in water) or decreases (turpentine, cane sugar in water, quinine in alcohol). Lastly, in the case of certain substances (aspartic acid, malic acid, invert sugar), it is found that as the temperature rises the rotation at first decreases, at a certain temperature becomes zero, then increases, but in the opposite direction. Thus, a solution of 17·21 grams of invert sugar in 100 c.c. is lævorotatory at the ordinary temperature, inactive at 87°, and above this it is dextrorotatory. The conclusion to be drawn from these facts is that heat brings about a certain change in the atomic grouping of active molecules.

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[1] For details on rotation-dispersion see Landolt, *Optisches Drehungsvermögen*, 1898, pp. 116–42, 378–90.

In order to be able to compare the rotatory powers of different active substances, the angles must relate not only to the same length of layer of liquid, but also to equal weights of the active substances in unit volume of the liquid.

If:

a denotes the observed angle of rotation,

l the length in decimetres of the polarimeter-tube,

S the number of grams of active substance contained in 1 c.c. of solution,

then the value which was introduced by Biot under the name *specific rotation* and denoted by $[a]$ is expressed by:

$$[a]=\frac{a}{l\,\mathrm{S}}.$$

The specific rotation is, therefore, that angle which a liquid shows when it contains one gram of active

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substance in 1 *c.c., and acts on polarised light by a layer* 1 *dm. in length.*

For homogeneous active liquids, S is replaced by the density d (weight in grams of 1 c.c.—specific gravity relatively to water at 4° as standard), and the formula becomes :

$$\text{I.} \quad . \quad . \quad . \quad . \quad . \quad . \quad [a]=\frac{a}{ld},$$

a and d being determined at the same temperature.

The specific rotation of such a substance is a characteristic constant, if the light used, the temperature, and the direction of the rotation are also given. Thus, for nicotine :

$$[a]_{\mathrm{D}}^{20}=-162{\cdot}8^{\circ}.$$

For solid active substances which are converted into the liquid state by means of an inactive and chemically indifferent solvent (water, alcohol, &c.), S may be determined in two different ways :

(a) In a small measuring flask of V c.c. capacity (the volume must be known in true cubic centimetres at some normal temperature—generally 20°—) m grams of the substance are dissolved in the solvent, and the solution diluted up to the mark. From this we calculate :

c, the concentration, *i.e.* the number of grams of active substance in 100 c.c. of solution,

then $\mathrm{S}=\frac{c}{100}$, and

$$\text{II.} \quad . \quad . \quad . \quad [a]=\frac{100a}{l\,c}, \text{ or also } [a]=\frac{a\,\mathrm{V}}{l\,m}.$$

(*b*) n grams of active substance are dissolved in f grams of inactive solvent in a stoppered flask, and the density, d, of the solution is determined by means of a pycnometer. We calculate:

$p=\frac{100\,n}{n+f}$, the percentage of active substance in 100 grams of solution,

then $S=\frac{p\,d}{100}$, and:

$$\text{III.} \quad . \quad . \quad . \quad . \quad . \quad [a]=\frac{100\,a}{l\,p\,d}.$$

This latter method is only applied when we desire to ascertain the dependence of the specific rotation on the composition of the solution. In very many cases the simpler formula II. suffices.

Data concerning the specific rotation of a solid substance must always be accompanied not only by the direction of the rotation, but also by:

(1) The kind of light used.

(2) The temperature at which a and d were determined.

(3) The solvent used.

(4) The concentration, c, of the solution, or the percentage, p, of dissolved substance. (In the latter case, it is advisable to give also d, in order that $c=p\,d$ may be calculated.)

As will be pointed out later, the influences of (3) and (4) on the rotatory power are often very great.

The form in which results of observations should be given, in order that the specific rotation $[a]$ may assume the value of a constant, can be gathered from the following examples:

CAMPHOR:

Alcohol . .	$p = 9{\cdot}69°$	$d^{20}_{4} = 0{\cdot}8094°$	$[\alpha]^{20}_{D} = +42{\cdot}81°$
,, . .	,, $= 49{\cdot}81$	,, $= 0{\cdot}8719$	,, $= +46{\cdot}93$
Acetic Acid .	,, $= 15{\cdot}88$	,, $= 1{\cdot}0339$	,, $= +44{\cdot}02$
,, ,, .	,, $= 65{\cdot}25$	,, $= 0{\cdot}989$	,, $= +50{\cdot}81$

d-TARTARIC ACID:

Water	$c = 5$	$[\alpha]^{20}_{D} = +14{\cdot}40$
Alcohol	,, $= 5$	,, $= +3{\cdot}79$
1 vol. alcohol + 1 vol. benzene	,, $= 5$	,, $= -4{\cdot}11$

STRYCHNINE:

Alcohol ($d = 0{\cdot}865$) . .	$c = 0{\cdot}91$	$[\alpha]^{18}_{D} = -128{\cdot}0$
Chloroform	,, $= 4{\cdot}0$	,, $= -130{\cdot}0$
,, ...	,, $= 1{\cdot}5$	,, $= -140{\cdot}7$

Molecular Rotation [M].—In order to compare the activity of different chemical compounds, the specific rotation must be referred to quantities which are in the relation of the molecular weights. In order to avoid large unwieldy numbers, the hundredth part of the product of specific rotation and molecular weight is taken, so that we have for the molecular rotation:

$$[M] = \frac{M}{100}[\alpha].$$

The molecular rotation, then, expresses the angle through which 1 mm. of the active substance, when in such a state that 1 c.c. contains 1 gram-molecule, would rotate a polarised ray.

5. Constant Specific Rotation of Dissolved Substances.—In 1835, in an investigation on the aqueous solutions of cane sugar, Biot[1] observed that the angle of rotation was proportional to the amount of sugar dissolved. In the case of turpentine oil dissolved in ether he was led to a similar conclusion. From the results of this investigation Biot formulated the following law: When an active substance is dissolved in an inactive liquid (no chemical action taking place between the two) the angle of rotation is proportional to the weight of active substance in unit volume of solution, and thus the specific rotation has a constant value.

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[1] Biot, *Mém. de l'Acad.* 13, 39.

According to our present knowledge this law of Biot has only a limited applicability. In the case of cane sugar solutions, later experiments have been carried out with more perfect polarisation apparatus, and it has been found that with increasing dilution of the solution the specific rotation increases; as the concentration c diminishes from 86 to 5 the value of $[\alpha]_D$ increases by 1·5 per cent.—namely, from $+65·62°$ to $66·61°$.

With some substances it has been found that within certain limits of concentration no regular increase or decrease of the value $[\alpha]$ takes place, but only small irregular variations which are to be attributed to experimental errors, so that for these the specific rotation may be regarded as constant. The following are some examples:

Milk sugar (with water of crystallisation) in water:
$p = 2·35$ to 36. Average $[\alpha]_D = +52·53°$ (observed 51·94° to 53·18°).

Rhamnose (with water of crystallisation) in water:
$c = 3$ to 30. Average $[\alpha]_D = +8·53°$ (obs. 8·48° to 8·65°).

Parasantonid in chloroform:

$p = 0{\cdot}14$ to 48. Average $[\alpha]_D = +890{\cdot}9°$ (obs. 887·9° to 896·5°).

Nicotine in benzene:

$p = 8{\cdot}5$ to 84·4. Average $[\alpha]_D = -164{\cdot}00°$ (obs. 164·29° to 163·67°).

Cocaine in chloroform:

$p = 10$ to 25. Average $[\alpha]_D = -16{\cdot}31°$ (obs. 16·28° to 16·36°).

6. Variation of Specific Rotation with Concentration.—In 1838 Biot[1] made the observation that with aqueous solutions of tartaric acid the specific rotation rises considerably with decreasing concentration, and in 1852 he found[2] the reverse variation in the case of other substances, as, for instance, solutions of camphor in alcohol or acetic acid, where the rotation diminishes as the dilution increases. The variation of $[\alpha]$ for cane sugar, as mentioned in Section 5, was also observed. Biot then called attention to the fact that in general the specific rotations deduced from solutions are more or less variable numbers, and that the molecule of the active substance appears to suffer some change in the presence of the inactive liquid.

This has since been substantiated for a very great number of substances, and now we know about an equal number of cases of increase and of decrease of specific rotation with increasing dilution. So far we do not recognise any connection between the direction of this variation and the chemical nature of the active substance, as may be gathered from the following examples:

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[1] Biot, *Mém. de l'Acad.* **15**, 93; *Ann. chim. phys.* [3] **10**, 385.

[2] Biot, *Ann. chim. phys.* [3] **36**, 257.

WITH INCREASING DILUTION OF THE SOLUTION THE SPECIFIC ROTATION

INCREASES:	DECREASES:
d-tartaric acid (in water). Sodium *d*-tartrate (water). *d*-(+) diacetyltartaric anhydride (acetone). *d*-(−) lactates } (aqueous alcohol). *d*-(+) lactates } Alkali *d*-cholalates (water). *d*-glucuronic acid (water). Sodium *d*-podocarpate (water).	Sodium hydrogen *d*-tartrate (water). Potassium *d*-tartrate (water). *d*-(+) diacetyltartaric acid (water, alcohol). *d*-camphoric acid (alcohol, acetic acid). *d*-camphorates (water). *d*-cholalic acid (alcohol). *l*-quinates (water). *l*-shikimic acid (water).
d-cinchonine (alcohol, chloroform). *d*-cinchonine salts (water, alcohol). *l*-apocinchonine hydrochloride (water). *d*-conchinine and salts (alcohol, water). *l*-quinine and salts (alcohol, water). *l*-cinchonidine and salts (alcohol, water). *l*-morphine salts (water). *l*-strychnine, brucine (chloroform). *l*-(−) cocaine (chloroform). *l*-(+) cocaine hydrochloride (alcohol).	*l*-β-isocinchonine (alcohol). *l*-β-isocinchonine hydrochloride (water). *l*-benzoyl cinchonine (alcohol). *l*-hyoscyamine (alcohol). *d*-conine (alcohol, benzene). *d*-conine salts (alcohol). *l*-(−) nicotine (water, alcohols, aniline, toluidine). *l*-(+) nicotine salts (water).
d-cane sugar (water). *d*-maltose (water). *l*-salicin (water).	*d*-dextrose (water). *l*-levulose (water). *d*-xylose and rhamnose (water). *l*-phloridzin (alcohol).

With Increasing Dilution of the Solution the Specific Rotation

Increases:	Decreases:
d-(−) α-nitrocamphor (benzene).	*d*-camphor (alcohols, acetic acid, acetic ether, monochloracetic ether, benzene, dimethylaniline).
d-pinene (alcohol).	*l*-cholesterine (chloroform).
l-pinene (alcohol, acetic acid, benzene).	
l-menthol (alcohol, acetic acid, benzene).	

The *cause* of the change of specific rotation with varying concentration differs according to the nature of the substances. This cause has been definitely recognised in a series of cases :

(*a*) For *electrolytes* there is a distinct connection between the increase or decrease of the rotation with increasing dilution, and the simultaneously increasing degree of electrolytic dissociation.

It was early observed (Landolt [1]) that equivalent quantities of different tartrates in dilute aqueous solution possessed almost the same rotation independent of the metal which they contained; and, further, that the specific rotation of different salts of an active alkaloid at sufficient dilution was also constant independent of the nature of the acid combined (Oudemans [2]). The following table exhibits this constancy:

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[1] Landolt, *Ber.* **6**, 1077 (1873).

[2] Oudemans, *Lieb. Ann.* **197**, 48, 66 (1879) ; **209**, 38 (1881) ; *Rec. Trav. chim. Pays Bas*, **4**, 166 (1886) ; Tykociner, *Rec. Trav. chim.* **1**, 144 (1883).

Tartrates (Landolt)		Quinates (Oudemans)			Quinamine (Oudemans)	Strychnine (Tykociner)
					1 mol. acid to 1 mol. base	
7·69 grams of tartaric acid in 100 cc.	$[M]^{20}_{D}$ of the salt	2·6 grams of quinic acid, $C_7H_{12}O_6$, in 100 c.c.	$[\alpha]_D$ of the acid	Acid	1·56 grams of base in 100 c.c. $[\alpha]^{16}_{D}$ of the base	0·46 grams of base in 100 c.c. $[\alpha]^{20}_{D}$ of the base
Li_2. $C_4H_4O_6$	+58°·1	K. $C_7H_{11}O_6$	−48°·8	HCl	+114°·4	−34°·1
$(NH_4)_2$,,	63·0	Na ,,	48·9	HNO_3	116·5	34·1
Na_2 ,,	59·9	NH_4 ,,	47·9	$HClO_3$	116·1	—
K_2 ,,	64·4	$Ba(C_7H_{11}O_6)_2$	46·6	H_2SO_4	116·4	35·3
$Na.NH_4$,,	61·7	Sr ,,	48·7	H_3PO_4	117·3	34·4
$K.NH_4$,,	63·8	Ca ,,	48·7	H_3AsO_4	—	33·9
K.Na ,,	62·3	Mg ,,	47·8	CH_2O_2	114·7	34·0
K.AsO ,,	58·8	Zn ,,	51·0	$C_2H_4O_2$	116·2	34·0
$K.C_2H_5$,,	64·6			$C_2H_2O_4$	118·1	33·1
½$Ba.C_2H_5$,,	63·0			$C_6H_8O_7$ (citric)	—	33·9
Mg ,,	61·7					

Hädrich[1] first called attention to the fact that the constancy of the rotation shown by the different salts of an active acid or base in equimolecular solution is easily understood if we assume that these electrolytes at great dilution are almost completely dissociated into their ions, so that all the solutions contain equal quantities of acid or base ions.

It has been observed in many cases that the specific rotation of active electrolytes (acids and salts) increases or decreases with decreasing concentration, but after a certain dilution has been reached it remains constant. Walden[2] has made a comparison of the rotation and the degree of dissociation (determined from the electric conductivity) of solutions of *a*-bromocamphor sulphonic acid $C_{10}H_{14}BrO.SO_3H$. The following are his results:

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[1] Hädrich, *Zt. ph. Chem.* **12**, 476 (1893). [See also Carrara and Gennari, *Zt. ph. Chem.* **17**, 561 (1895).]

[2] Walden, *Zt. ph. Chem.* **15**, 196 (1894).

C	α_D^{20} for l=4dm	$[\alpha]_D^{20}$	$[M]_D^{20}$	Percentage degree of dissociation
14·952	+55°·20	+92°·3	+287°	68·5
1·037	3·64	87·7	273	92·7
0·518	1·795	86·6	269	94·4
0·259	0·901	86·9	270	95·5

The acid ion has, therefore, a lower rotatory power than the original acid.

If the degree of dissociation of an active electrolyte be diminished by adding to the solution an inactive electrolyte a change of rotation takes place. Thus by the addition of mineral acids to a solution of tartaric acid or of alkaloid salts the rotation is diminished. In the same way alkalis decrease the activity of tartrates.

If an active electrolyte be dissolved in a liquid such as alcohol, acetone, &c., which has a smaller dissociating power than water, the rotation of the solution differs from that of an aqueous solution; the value of the rotation is greater or less according as the active ion has a weaker or a stronger rotatory power than the unchanged substance. Thus Walden[1] has shown that the rotatory power of *a*-bromocamphor sulphonic acid, as well as that of its barium salt, increases considerably on the addition of acetone to the aqueous solution on account of the diminution of the dissociation, whereby more acid molecules are produced, and these have a greater rotatory power than the acid ion.

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[1] Walden, *Zt. ph. Chem.* 15, 205 (1894).

The rotation of salts composed of an active acid and an active base must, in dilute solution, be equal to the sum of the rotation values of the anions and the cations. This has been confirmed by Walden for morphine and cinchonine *a*-bromocamphor sulphonates.

Lastly, it is to be mentioned that in the case of salts of very weak acids and bases besides the electrolytic, also hydrolytic dissociation may take place whereby the number of active atom-complexes present in the liquid is further increased. According to Hädrich,[1] hydrolysis seems to take place in the solutions of the dihydrochlorides of cinchonidine and cinchonine, inasmuch as no constant value for the rotation is arrived at on progressively increasing the dilution as is attained with the monohydrochlorides.

(*b*) In the case of weak electrolytes and nonelectrolytes the cause of the variation of their rotatory power has been sought in the formation and decomposition of polymerised molecules. Molecular weight determinations, by the freezing and boiling point methods, have demonstrated that many liquid as well as solid bodies in solution in certain solvents appear as single molecules, and in other solvents they are present as double molecules (*e.g.* acetic acid in ether $= C_2H_4O_2$, in benzene $= C_4H_8O_4$). Attempts have been made to find if the influence which different solvents or differences of concentration exert on the specific rotation of active substances is in any way connected with the variation of the molecular weight of the latter.

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[1] Hädrich, *Zt. ph. Chem.* **12**, 491 (1893).

The investigations on this subject[1] have not as yet led to any law directly connecting the variation of the rotation and of the molecular weight. Many substances show very widely varying specific rotations when dissolved in different solvents (*e.g.* *l*-mandelic ethyl ester in acetone $[\alpha]_D = -90{\cdot}6°$, in chloroform $-180{\cdot}0°$), whilst the molecular weights found are the same, and indeed normal. With other substances both the molecular weight and the rotation vary, but in opposite directions. Thus liquid propyl tartrate of normal molecular weight $M = 234$ and $[\alpha]_D = +12{\cdot}4°$ has in benzene solution $M = 306$ and $[\alpha]_D = +20{\cdot}1°$, but in ethylene bromide solution $M = 326$ and $[\alpha]_D = -0{\cdot}6°$. In both solutions the molecular weight has increased, showing that a partial polymerisation to double molecules has taken place, but the optical action has not varied in both in the same direction: in the first solvent the rotation of the original substance has increased by about 8·7°; in the second it has suffered a decrease of about 13°.

With itaconic diamyl ester the influence of molecular association could be directly observed. This substance when freshly prepared is a liquid, but after some time it polymerises to a solid. Walden[1] has found the following angles of rotation of it in the different states ($l=1$ dm.):

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[1] See the details in Landolt's *Das optische Drehungsvermögen*, 2nd edition, pp. 201–205.

Freshly prepared: mobile liquid	$\alpha_D = +\overset{\circ}{4}{\cdot}80$
After two months: viscid liquid	$,, = +4{\cdot}75$
Quite hard: colourless glass	$,, = +4{\cdot}75$

Here, therefore, there is no evidence of any influence of polymerisation on the rotatory power.

Besides, it does not seem reasonable to suppose that by the association of only two molecules (or where the association-factor is less than two) the original rotatory power should be altered. On the other hand, when a large number of single molecules combine to a crystal-molecule which possesses either a dextro- or a lævo- structure, we should expect some variation of the original rotation. It has already been mentioned, in Section 2, that for those substances which are active both in the dissolved and in the crystalline state, the rotatory power in the latter form is composed of the action of the single molecules and of the crystal-molecules. If it may be assumed that at least in concentrated solutions of solid active substances such complicated aggregates are formed which are split up to normal molecules by progressive dilution, then the variation of the rotation of certain substances might be explained.

This is the case for the phenomena which have been observed with aqueous solutions of malic acid and tartaric acid. Ordinary malic acid and its alkali-salts have a lævorotation in dilute solution, which, with increasing concentration, diminishes, then passes through the inactive point to an increasing dextrorotation (Schneider[1]). The same takes place on lowering the temperature (Thomsen[2]). The following is a table of Schneider's and Thomsen's results, in which p denotes the percentage of dissolved active substance:—

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[1] Walden, *Zt. ph. Chem.* **20**, 383 (1896).

Malic acid		Sodium malate		Malic acid		
p	$[\alpha]_D^{20}$	p	$[\alpha]_D^{20}$	Temp.	$p=28{\cdot}67$ $[\alpha]_D$	$p=40{\cdot}44$ $[\alpha]_D$
	°		°	°	°	°
8·32	−2·30	5·27	−8·39			
16·65	−1·58	14·66	−6·98			
29·06	−0·63	25·27	−5·28	30	−0·83	−0·12
29·69	−0·34	29·99	−4·34	20	−0·35	+0·54
35·26	−0·04	33·91	−3·43	10	+0·33	+1·31
36·66	+0·09	42·22	−1·26			
37·53	+0·17	46·84	−0·16			
46·67	+1·00	48·79	+0·50			
59·99	+2·31	55·26	+2·15			
70·12	+3·34	65·53	+4·72			

With *d*-tartaric acid the reverse takes place, the dextro- passing into a lævorotation when the concentration becomes very great. Thus for the blue ray ($\lambda=438{\cdot}3\ \mu\mu$) a 60 per cent. solution has $[\alpha]=+2{\cdot}92$, a 70 per cent. solution $-0{\cdot}23°$.

The reversion of rotation cannot be explained (1) by electrolytic dissociation, because it has been found from conductivity experiments that this only takes place at very great dilution; (2) by association of two or more molecules, because cryoscopic determinations with malic acid solutions up to the concentration $p=24\cdot5$ have always led to the normal molecular weight. The phenomenon can be explained, however, by assuming that the lævorotatory single molecules of malic acid combine on increasing concentration to dextrorotatory aggregates; or the dextrorotatory tartaric acid molecules combine to lævorotatory crystal-aggregates. If this be true, then anhydrous malic acid must be dextrorotatory and anhydrous tartaric acid lævorotatory. For tartaric acid this has proved to be the case, especially with rubidium *d*-tartrate, which separates out from the dextrorotatory solution in lævorotatory crystals; and lævorotatory solutions of rubidium *l*-tartrate yield dextrorotatory crystals (Wyrouboff[1]; H. Traube[2]). No one has yet succeeded in conclusively proving the presence of such active crystal-molecules in a liquid.

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[1] Schnieder, *Lieb. Ann.* **207**, 257 (1881).

[2] Th. Thomsen, *Ber.* **15**, 441 (1882).

An explanation of the increase of the rotation of tartaric acid by increasing dilution has also been brought forward, based on the supposition that an increasing number of acid molecules are transformed into hydrates of definite or varying composition whereby the activity is increased (Biot[3]). It has further been assumed with other substances that loose compounds with the solvent are formed. The presence of such associated molecules has not been proved by cryoscopic or other methods, and Nernst[4] has shown that an increasing formation or decomposition of hydrates by progressive dilution is not possible, but rather that at every concentration the proportion of hydrated to non-hydrated molecules must be the same.

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[1] Wyrouboff, *Journal de Physique* [3] **3**, 451 (1894).

[2] H. Traube, *Sitz.-Ber. d. Berl. Akad.* **1**, 195 (1895).

[3] Biot, *Mém. de l'Inst.* I., **15** (1838).

[4] Nernst, *Zt. ph. Chem.* **11**, 345 (1893).

In certain cases the production of hydrates certainly takes place—thus, *e.g.* with nicotine, where the evolution of heat on mixing with water, as well as the fact that nicotine solutions of moderate concentration (30 to 70 per cent.) separate out the base as an oil on heating, show that this formation occurs. The densities of mixtures of nicotine with increasing quantities of water, increase up to a maximum reached with about 69 per cent. of nicotine (corresponding to the hydrate $C_{10}H_{14}N_2 + 4H_2O$), then diminish. The fact that the specific rotation of the nicotine down to this point, when represented graphically, has a steeper course than in the more dilute solutions in which the optically active molecules are nicotine hydrate may be regarded as in agreement with these density observations (Pribram and Glücksmann[1]).

It is quite evident that the rotation of an active substance in solution in a liquid where a stable chemical compound is formed, *e.g.* a solution of borneol in chloral or bromal, will be quite different from the rotation in an indifferent solvent.

For the explanation of the increase or decrease which the rotation of non-electrolytes suffers by the presence of solvents, there remains for the majority of substances only the following assumption, which cannot, however, be experimentally confirmed. It may be imagined that when molecules of solvent (*e.g.* alcohol) enter into the spaces between the molecules of an active substance (*e.g.* turpentine oil) which all exert the same attraction on each other, a certain modification of the original structure is brought about, because the solvent molecules exert a different attractive force. The result of this is that in every molecule the relative distance of the atoms, their arrangement in space, and their motion, will be altered. The asymmetry in the density of the ether—which conditions the activity—will also be modified, and the alterations will be the greater as the number of inactive molecules increases. If the active substance be dissolved in various indifferent solvents, varying rotations will result, because different kinds of molecules have different attractive powers.

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[1] Pribram and Glücksmann, *Sitz.-Ber. d. Wien. Akad.* **106**, II. *b* June 1897. The greatest density was formerly assumed to correspond to the nicotine hydrate $C_{10}H_{14}N_2 + 5H_2O$.

7. Derivation of the True Specific Rotation of Dissolved Substances.—The variation of the specific rotation of an active substance can best be seen in a graphic representation of the results obtained from a series of solutions of different concentrations, by plotting on the abscissæ-axis the percentage of inactive solvent, (q), and raising ordinates proportional in length to the corresponding value of $[a]$. The increase or decrease of the specific rotation

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is in some cases represented by a straight line—it runs, therefore, proportional to q—and may be expressed by the formula :

$$\text{I.} \quad . \quad . \quad . \quad . \quad . \quad [\alpha]=\text{A}+\text{B}q,$$

the constants of which, A and B, may be calculated from the results obtained. In other cases a curve is obtained which generally forms a portion of a parabola or of a hyperbola, and then the dependence of the specific rotation on q may be expressed in one or other of the forms :

$$\text{II.} \quad . \quad . \quad [\alpha]=\text{A}+\text{B}q+\text{C}q^2 \text{ or } [\alpha]=\text{A}+\frac{\text{B}q}{\text{C}+q},$$

or by some other formula containing several constants.

In these formulæ A is the specific rotation of the pure substance, and the values of B (I.) or B and C (II.) represent the increase or decrease which the substance suffers by the action of 1 per cent. of inactive solvent.

If we set $q=0$ we get the specific rotation of the pure substance; but if in formula I. or II. we set $q=100$, we obtain for $[\alpha]$ a value which may be regarded as the specific rotation of the active substance at infinite dilution. If we assume that in the case where $q=100$ the active substance has completely disappeared, and that the liquid consists entirely of inactive solvent, then the rotatory power must become zero. This may also, according to Biot, be derived from the above expressions by comparing them with the formula: $[\alpha]=\frac{\alpha.100}{l.\,d.p}$, by means of which the specific rotation is calculated from the observed angle of rotation. If in this formula we replace p by $100-q$ (since $p+q=100$), then, making use of I., we see that:

$$\frac{a.100}{l.d.(100-q)}=\mathrm{A}+\mathrm{B}q,$$

and, therefore:

$$a=l.d.\left[\mathrm{A}+\left(\mathrm{B}-\frac{\mathrm{A}}{100}\right)q-\frac{\mathrm{B}}{100}q^2\right].$$

If now in this equation we set $q=100$, then a becomes zero, *i.e.* the rotatory power has entirely disappeared. If, on the other hand, we set $q=0$, then a remains equal to $l.\ d.\ \mathrm{A}$—namely, the angle of rotation which a layer of l dm. of the pure substance with density d would show. It follows that $\frac{a}{l.d}=\mathrm{A}$, and since $\frac{a}{l.d.}=[a]$, therefore $[a]=\mathrm{A}$. That is to say, A is the specific rotation of the substance in the absence of solvent.

With active liquid substances which are miscible in all proportions with an indifferent solvent, the variation from the original specific rotation up to extremely dilute solutions can be experimentally determined, *i.e.* all parts of the curve from $q=0$ up to nearly $q=100$. If the constant A be calculated from the results of a number of solutions, the value will agree more exactly with the specific rotation of the pure substance the greater the part of the curve covered by the observations, and the nearer they are to the abscissæ $q=0$, *i.e.* the more concentrated the solutions.

The following are some results of this nature (Landolt [1]):

TURPENTINE OIL (lævorotatory).

(a) Without solvent . . . . $[\alpha]_{\mathrm{D}}^{20} = \overset{\circ}{3}7{\cdot}01$

$$\text{(b) Dissolved in} \left\{ \begin{array}{lll} \text{alcohol} & (q=10 \text{ to } 90) & ,, \; = 36{\cdot}97 + 0{\cdot}0_2482q \\ & & \qquad + 0{\cdot}0_3133q^2 \\ \text{benzene} & (q=10 \text{ to } 90) & ,, \; = 36{\cdot}97 + 0{\cdot}0215q \\ & & \qquad + 0{\cdot}0_4667q^2 \\ \text{acetic acid} & (q=10 \text{ to } 90) & ,, \; = 36{\cdot}89 + 0{\cdot}0246q \\ & & \qquad + 0{\cdot}0_3137q^2. \end{array} \right.$$

TURPENTINE OIL (dextrorotatory).

(a) Without solvent . . . . $[\alpha]_{\mathrm{D}}^{20} = 14{\cdot}15$

(b) Dissolved in alcohol ($q=27$ to 78) . ,, $= 14{\cdot}17 + 0{\cdot}0118q$.

NICOTINE (lævorotatory).

(a) Without solvent . . . . $[\alpha]_{\mathrm{D}}^{20} = 161{\cdot}55$

(b) Dissolved in alcohol ($q=10$ to 85) . ,, $= 160{\cdot}83 - 0{\cdot}2224q$.

ETHYL TARTRATE (dextrorotatory).

(a) Without solvent . . . . $[\alpha]_{\mathrm{D}}^{20} = 8{\cdot}31$

$$\text{(b) Dissolved in} \left\{ \begin{array}{lll} \text{alcohol} & (q=22 \text{ to } 78) & ,, \; = 8{\cdot}41 + 0{\cdot}0187q \\ \text{acetic acid} & (q=22 \text{ to } 85) & ,, \; = 8{\cdot}42 + 0{\cdot}0625q \\ & & \qquad - 0{\cdot}0_3348q^2 \\ \text{water} & (q=20 \text{ to } 86) & ,, \; = 8{\cdot}09 + 0{\cdot}2003q \end{array} \right.$$

It is evident, therefore, that the specific rotation of the original substance may be derived, with a very close approximation, from observations on solutions.

When the active substance is solid, the actual rotatory power cannot be determined directly, and, according to its solubility, only a greater or smaller part of the curve can be found, which part must necessarily start at a certain distance from the origin of the system of coordinates. If the constants of formulæ I. and II. be calculated from the direct observations, then these values may only strictly be used for intrapolation within the limits of dilution over which the solutions experimented upon extend.

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[1] Landolt, *Lieb. Ann.* 189, 311 (1877).

The question now arises: In how far may we regard the value found for the constant A as the specific rotation of the pure substance? The extrapolation thus carried out will be valid if the variation of rotation is represented by a straight line—*i.e.* by the formula $[a]=A+Bq$. If, on the other hand, it is represented by a curve, then the value of A calculated from the equation $[a]=A+Bq+Cq^2$, (or some other equation), will vary from the true specific rotation the smaller the part of the curve determined. The exactitude which can be attained by this method depends, therefore, on the solubility of the active substance in the solvent employed. If the solubility is very low, so that only very dilute solutions can be obtained, and if the increase or decrease of the values for $[a]$ is not proportional to the differences of q, then it is impossible to derive the specific rotation of the pure substance.

For the experimental proof of these assertions camphor was chosen, and was dissolved in various solvents. With each solvent the most concentrated possible and several diluter solutions were prepared, and the rotation of each taken. The following are the intrapolation-formulæ obtained:

CAMPHOR (dextrorotatory).

Dissolved in	$q =$ Per cent.	$[\alpha]_D^{20} =$
Acetic acid . . .	35 to 84	$55{\cdot}49 - 0{\cdot}1372q$
Acetic ether . .	46 to 85	$55{\cdot}15 - 0{\cdot}0438q$
Monochloracetic ether	46 to 86	$55{\cdot}70 - 0{\cdot}0668q$
Benzene . . .	37 to 76	$55{\cdot}21 - 0{\cdot}1630q$
Dimethylaniline . .	43 to 85	$55{\cdot}78 - 0{\cdot}1491q$
Methyl alcohol . .	50 to 89	$56{\cdot}15 - 0{\cdot}1749q + 0{\cdot}0_3662q^2$
Ethyl alcohol . .	45 to 90	$54{\cdot}38 - 0{\cdot}1614q + 0{\cdot}0_3369q^2$
	Mean .	$55{\cdot}4 \pm 0{\cdot}4$

Although the most concentrated solutions employed did not contain more than 54 to 65 per cent. of camphor, yet the values obtained for the constant A agree fairly well, and the mean value, 55·4°, may with certainty be assumed as the rotation of pure camphor.

The numbers for the specific rotation obtained by the above method express the action of the molecules, and refer to the substance in the amorphous condition with density =1. If the same substance were investigated in the crystalline state, an abnormal result might be obtained in consequence of the influence of crystal rotation. This may be ascertained in the case of camphor, for the angle of rotation α_D of a section 1 mm. thick, cut perpendicularly to the optical axis, is +0·65°, and the density is 0·998. The specific rotation of a layer 1 dm. long is, therefore, $[\alpha]_D = \frac{100 \times 0{\cdot}65}{0{\cdot}998} = 65{\cdot}1^\circ$. This number must be the sum of the molecular rotation (55·4°), and the crystal rotation, which latter is found to be $65{\cdot}1 - 55{\cdot}4 = 9{\cdot}7^\circ$.

In the case of electrolytes the best results to use for the comparison of their activities are those calculated from the intrapolation-formulæ, in which q is set equal to 100, *i.e.* the results corresponding to solutions of infinite dilution. We thus ascertain the specific rotation of the ions.

[From an investigation on mandelic acid and its sodium salt, Rimbach, *Zt. ph. Chem.* **28**, 251 (1899), concludes that the extrapolation gives exact results for strong electrolytes, but for weak electrolytes it may lead to quite a wrong value.]

8. Addition of Inactive Substances to the Solution of an Active Compound.—According to the nature of the two substances, either an increase or a decrease of the rotation may occur, the cause of which in certain cases is the alteration in the degree of dissociation, in others the formation of chemical compounds. Our present knowledge of this phenomenon is restricted to the following substances:

(*a*) Tartaric acid and malic acid. It has been found that, by the addition of inorganic compounds, the specific rotation of these substances suffers a change, generally small, but sometimes quite considerable.

The alkali salts exert only a weak action on the tartrates, which is to be attributed to the diminution of the degree of dissociation of these latter, but which in different cases, strange to say, makes itself felt in opposite directions. Thus the rotation of potassium sodium tartrate is slightly increased by the addition of neutral potassium or ammonium salts, but is diminished by sodium salts (Long).

The activity of free tartaric acid is greatly increased (three to four times) by the addition of boric acid (Biot). This is due to the formation of boryltartaric acid, $H.(BO)C_4H_4O_6$, which has a high rotation. Malic acid behaves in the same way. The alkali boryl-, arsenyl-, and antimonyl-tartrates, *e.g.* tartar emetic, possess a very much higher rotation than the alkali tartrates. In the case of all such compounds the activity diminishes with increasing dilution, on account of hydrolytic decomposition.

The greatest increase in the rotatory power of tartaric acid (twenty to sixty times the rotation of the acid in solution in pure water) is produced by the addition of alkali molybdates and tungstates. If these be added in increasing quantities to a solution of *d*-tartaric acid, the dextrorotation rises continuously to a maximum which is reached when there is a certain molecular proportion of the two substances present in the solution. Gernez made an extended series of experiments on solutions which contained in 100 c.c. 2·5 grams of tartaric acid and different quantities of the molybdates and tungstates. The following table gives the observed maximum rotation and the corresponding molecular proportion of tartaric acid and the salts :

	$[\alpha]_D$
Tartaric acid without the addition of salt . .	+ 13°·6
3 mol. tartaric acid + 1 mol. $(NH_4)_6Mo_7O_{24}+4aq$.	+ 781
1 „ „ „ + 1 „ Na_2MoO_4+2aq .	+ 517
1 „ „ „ + 2 „ Li_2MoO_4 . . .	+ 484
1 „ „ „ + 2 „ $MgMoO_4$ . . .	+ 523
1 „ „ „ + 1 „ K_2WO_4 . . .	+ 327
1 „ „ „ + 1 „ Na_2WO_4+2aq . .	+ 277

The rotation of malic acid is also changed by the addition of alkali tungstates, molybdates, or phosphomolybdates. The following table gives the results of two series of Gernez's experiments—with ammonium molybdate $(NH_4)_6Mo_7O_{24} + 4aq$, and with sodium molybdate $Na_2MoO_4 + 2aq$. 1·1166 grams of malic acid and increasing quantities *P* of the salt were dissolved in water, and the solution made up to 12 c.c. The angle of rotation α_D was determined in a tube 1·057 dm. long, and from this the specific rotation $[\alpha]_D$ given was calculated.

Ammonium molybdate				Sodium molybdate			
Grams of salt *P*	α_D^{17}	$[\alpha]_D^{17}$	Z	Grams of salt P	α_D^{17}	$[\alpha]_D^{17}$	Z
0·0	− 0°·20	− 2°·0		0·0	− 0°·20	− 2°·0	
0·013	− 0·40	− 4·1		0·084	− 1·12	− 11·4	
0·054	− 0·97	− 9·9		0·336	− 3·72	− 37·8	
0·107	− 1·70	− 17·3		0·504	− 5·48	− 55·7	
0·191	− 2·75	− 28·0		0·672	− 7·25	− 73·7	
0·282	− 3·82	− 38·8		1·008 = $\frac{1}{2}$ mol.	− 9·07	− 92·1	M_1
0·429	− 4·95	− 50·3		1·176	− 5·20	− 52·9	
0·572 = $\frac{1}{18}$ mol.	− 5·32	− 54·1	M_1	1·344	− 1·52	− 15·5	R_1
0·644	− 4·93	− 50·1		1·513	+ 3·02	+ 30·7	
0·736	− 4·17	− 42·4		1·848	+ 11·03	+ 112·2	
0·792	− 3·40	− 34·6		2·017 = 1 "	+ 14·02	+ 142·5	M_2
0·936	− 1·00	− 10·2		2·353	+ 8·68	+ 88·2	
0·966	− 0·42	− 4·3	*R*	2·689	+ 2·62	+ 26·6	
1·030 = $\frac{1}{10}$ "	+ 0·83	+ 8·4		2·857	+ 0·32	+ 3·3	R_2
1·144	+ 3·23	+ 32·8		3·025 = 1·5 "	− 0·83	− 8·4	
1·288	+ 7·20	+ 73·2		3·529 = 1·75 "	− 1·55	− 15·8	M_3
1·395	+ 10·35	+ 105·3		3·865	− 1·00	− 10·2	
1·717 = $\frac{1}{6}$ "	+ 20·92	+ 212·7		4·033 = 2 "	− 0·50	− 5·1	
2·146	+ 36·22	+ 368·2		4·201	0·0	0·0	R_3
2·575 = $\frac{1}{4}$ "	+ 52·47	+ 533·5		4·538	+ 0·87	+ 8·8	
3·863	+ 72·00	+ 731·9		5·042	+ 2·27	+ 19·3	
5·150 = $\frac{1}{2}$ "	+ 72·80	+ 740·1	M_2	5·546	+ 3·95	+ 40·2	
6·008	+ 72·33	+ 735·3		7·058	+ 7·17	+ 72·9	
6·438	+ 72·00	+ 731·9		8·067 = 4 "	+ 10·25	+ 104·2	

The relationship in the case of malic acid is much more complicated than with tartaric acid. In the column Z the letters *M* and *R* denote maximum and reversal points of the rotation, and it is seen that several of these occur. Increasing quantities of ammonium molybdate produce at first an increase of the original lævorotation up to a maximum (M_1); then a diminution and a transition (*R*) to a dextrorotation, which increases rapidly to a maximum (M_2); and finally a slow decrease of the dextrorotation. With sodium molybdate there occur three maximum-points (two of lævo- and one of dextrorotation), and at three different concentrations the rotatory power entirely disappears. The curve representing this change has a zigzag form. It may be further remarked that the characteristic points *M* and *R* generally coincide with concentrations at which there is a certain simple molecular proportionality between the malic acid and the salt present.

Walden[1] has shown that the rotation of tartaric acid and malic acid, as well as of other substances, may be very greatly increased by the presence of uranyl salts. If caustic potash solution, 10 grams in 100 c.c., and uranyl nitrate, 40 grams of $UO_2(NO_3)_2 + 6aq$ in 100 c.c., be added to the solution of the active acid, then the rotation reaches a maximum when the proportion of substances is 1 molecule at least of uranyl salt to 1 molecule of oxyacid, and so many molecules of potash as are required for the neutralisation of the $-COOH$ and $-NO_3$ groups present. For an oxy-monocarboxylic acid 3 molecules of potash, and for an oxy-dicarboxylic acid 4 molecules, are necessary.

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[1] Walden, *Ber.* 30, 2889 (1897).

The following table contains Walden's results :

	Acid in 100 c.c. of solution	Solution in pure water		Maximum rotation in presence of caustic potash and uranyl nitrate	
		α_D for 2 dm.	$[\alpha]_D$	α_D for 2 dm.	$[\alpha]_D$
	gm.				
l-malic acid . .	0·65	−0°·01	− 0°·77	−6°·17	−475°
d-tartaric acid . .	0·75	+0·22	+ 14·7	+4·55	+303
d-methyltartaric acid .	0·965	+0·35	+ 18·0	+4·48	+232
l-quinic acid . .	0·96	−0·79	− 41·0	−1·96	−102
l-mandelic acid . .	0·76	−2·30	−151·3	−5·12	−337

The original direction of the rotation of these acids is, therefore, not reversed by the uranyl salt, but is very greatly increased.

The action of the uranyl salts, as also of the molybdates and tungstates, must be attributed to the formation of salts of complex acids, which are endowed with a very high rotatory power. The formation of such compounds is connected with the presence of a $>$CH.OH group in the organic acids, and it does not take place when this group is absent, as, for instance, in chlorosuccinic, bromosuccinic, and amylacetic acids. As Walden has shown, uranyl nitrate exerts no increasing effect on the rotation of these latter acids. It would also appear that the high activity of the solutions is not connected with dissociation phenomena, for the action of uranyl salts on malic, tartaric, and quinic acids is almost as great in alcoholic as in aqueous solution.

(*b*) Sugars.

The rotation of cane sugar in aqueous solution ($[\alpha]_D$=about +66·5°) is reduced to nearly 60° by the presence of neutral inorganic salts of the alkalis or alkaline earths. Borax also produces a decrease. The action of all these salts increases with the amount present.

Calcium chloride increases the specific rotation of dextrose from about 55° to 60° when it is present in the solution to the extent of 20 per cent.

The compounds of the mannitol group (arabitol, mannitol, sorbitol, talitol, mannoheptitol, &c.), which exhibit hardly any rotatory power in pure aqueous solution, become highly active on the addition of borax. In this way the specific rotation of *d*-mannitol may be raised to +28·3°. Borax is often used to make the activity more evident.

Free molybdic acid, acid sodium molybdate $Na_6Mo_7O_{24}$, and ammonium molybdate $(NH_4)_6Mo_7O_{24}$, also increase the rotation of these sugars; that of *d*-mannitol may thus be raised to $[\alpha]_D = +43{\cdot}2°$.

The action of borax on the members of this group is probably due to the same cause as that explained in connection with tartaric acid—namely, to the formation of boryl compounds. In the case of the molybdates, the molybdenum probably passes into the sugar molecule.

9. Change of the Rotatory Power of Dissolved Substances with Time. Multirotation. — The peculiar phenomenon of the angle of rotation of freshly prepared solutions, either increasing or decreasing towards a constant value, is exhibited by certain substances. The interval during which the change takes place is generally some hours, but it may be considerably shortened by boiling the solution. The substances which have this property are:

1. A series of sugars.
2. Certain oxyacids and their lactones.

In 1864 Dubrunfaut observed that the rotation of a solution of grape sugar (*d*-glucose), on standing for some time, diminished to about half of its original value. For the high initial rotation the term *birotation* was introduced; but this, upon the suggestion of Tollens, was altered to *multirotation* when it was discovered that with other sugars the ratio of the final constant rotation to the initial rotation was different from that found in the case of grape sugar.

It was further discovered (by Schmöger) that ordinary milk sugar, which shows birotation (decrease of a on standing), may by dehydration be converted into another modification, and the rotation of a solution of this increases. The term *hemirotation* is applied to an initially low rotation, such as that exhibited by this dehydrated modification. Tollens has further suggested the terms *more-rotation* and *less-rotation* for the two kinds of multirotation.

It has been shown, particularly in the case of *d*-glucose, *d*-galactose, rhamnose, and milk sugar, that the alteration of the rotation is due to the existence of three different isomeric modifications. These are denoted as α, β, and γ; the α and γ varieties are unstable in aqueous solution, and readily pass into the β-modification, the completion of the change being recognised by the rotation becoming constant. If the intensity of the activity decreases in the order $\alpha>\beta>\gamma$, then it is evident that the α-form exhibits *more-rotation* and the γ-form *less-rotation.* In the case of the four sugars mentioned, all three modifications are known; only the α- and β-forms of other sugars, such as arabinose, xylose, fructose, &c., have, so far, been recognised. The following table gives the specific rotations (calculated for the water-free crystals) of the different modifications of a number of sugars. In the column C the concentration of the substance (grams per 100 c.c. of solution) is given.

Sugar		C	Modification		
			$\alpha \rightarrow$ Initial rotation $[\alpha]_D^{20}$	β Final rotation $[\alpha]_D^{20}$	$\leftarrow \gamma$ Initial rotation $[\alpha]_D^{20}$
$C_5H_{10}O_5$	*l*-arabinose	9·7	+157°	+104·6°	—°
	l-xylose	10	+ 86	+ 19·0	—
$C_6H_{12}O_6$	*d*-glucose	9	+105	+ 52·5	+ 22·5
	l-glucose	4·2	− 95	− 51·4	—
	d-galactose	10	+135	+ 81·6	+ 52
	d-fructose	10	−104	− 92·3	—
$C_6H_{12}O_5$	fucose	6·9	−112	− 77·0	—
	rhamnose	10	− 5	+ 9·2	+ 23
$C_7H_{14}O_6$	rhamnohexose	10	− 83	− 61·4	—
$C_7H_{14}O_7$	α-glucoheptose	10	− 25	− 19·7	—
	d-mannoheptose	10	+ 85	+ 68·6	—
$C_8H_{16}O_8$	α-glucooctose	6·6	− 62	− 43·9	—
$C_{12}H_{22}O_{11}$	milk sugar	7	+ 88	+ 55·3	+ 36
	maltose	10	—	+137·0	+124

The true rotation of the unstable α- and γ-modifications cannot be exactly determined, because a certain time must necessarily elapse between making up the solution and the polarimetric examination, and during this time the change to the β-form will have progressed to a slight extent. The observed rotation for the α-form will be too small, and for the γ- too large. For the stable β-form, of course, the exact value can be ascertained.

The ordinary preparation of any of these sugars obtained by crystallisation from water is the α-form. The β-modification can usually be obtained by evaporating a solution of the α- or γ-form to dryness on the water-bath, or by precipitating the concentrated solution with alcohol, whereby it is obtained crystalline. In the case of *d*-glucose it has been shown that if a solution of the β-variety be allowed to evaporate, crystals of the α-isomer separate out; but these are formed just at the moment of crystallisation, for the mother liquor still shows the rotation of the β-isomer. The γ-isomers of glucose, rhamnose, and milk sugar have been obtained by quick evaporation of a solution of the α-compound and heating the residue to between 90° and 110°. By re-crystallisation the γ-form yields the α-isomer (Schmöger,[1] Tanret[2]).

According to experiments with glucose and milk sugar, the change of the α- into the β-modification agrees with the well-known speed formula of

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[1] Schmöger, *Ber.* **13**, 1915, 2130 (1880); **14**, 2121 (1881).

[2] Tanret, *C. r.* **120**, 1060 (1895); *Bull.* [3] **15**, 195, 202 (1896).

Wilhelmy for reactions of the first order. The transition may be accelerated by the addition of acids or bases; thus, if a small quantity of ammonia be added, a constant rotation is obtained after a few minutes. Salts also favour the change, with the exception of sodium chloride, which exerts a retarding influence.

The existence of these three modifications of a sugar is probably to be accounted for by structure-isomerism or stereoisomerism, but a proof of this is still wanting. Cryoscopic investigation has shown that all three have the same molecular weight.

Multirotation of certain oxyacids and their lactones was first observed by Wislicenus with lactic acid, and later by Tollens with saccharic, gluconic, galactonic, arabonic, xylonic, rhamnonic acids, &c. The lactones invariably possess a higher rotatory power than the acids themselves, and the rotation of an aqueous solution of the lactone continuously decreases until a constant value is reached. On the other hand, a fresh solution of the acid (prepared by decomposing a salt with hydrochloric acid) suffers a gradual increase of its rotation up to a constant value which is the same as the diminished rotation of the lactone solution.

The explanation of this is that, in aqueous solution, the lactone is partially transformed to the acid, and, inversely, the acid to lactone, and a final state of equilibrium is reached at which the two occur in the solution in a certain definite proportion.

The following are the results, showing such a change of rotation, obtained from solutions of *d*-saccharic acid and its lactone at the ordinary temperature. The time required for the establishment of the state of equilibrium is easily seen.

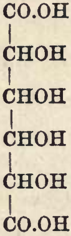
d-saccharic acid, $C_6H_{10}O_8$. Acid ammonium salt and hydrochloric acid. C=4·634 grams acid=4·237 grams lactone.		Saccharic acid lactone, $C_6H_8O_7$. Weighed directly. C=10·213 grams lactone.	
Initially .	. $[\alpha]_D = +9^\circ\cdot1$	Initially .	. $[\alpha]_D = +37^\circ\cdot9$
After 1 day .	,, = 11·0	After 4 days .	,, = 32·3
,, 2 days .	,, = 13·2	,, 6 ,, .	,, = 30·5
,, 4 ,, .	,, = 15·5	,, 11 ,, .	,, = 26·3
,, 5 ,, .	,, = 16·4	,, 14 ,, .	,, = 24·9
,, 6 ,, .	,, = 17·2	,, 18 ,, .	,, = 24·1
,, 8 ,, .	,, = 18·5	,, 25 ,, .	,, = 23·2
,, 12 ,, .	,, = 20·5	,, 28 ,, .	,, = 23·1
,, 14 ,, .	,, = 20·8	,, 32 ,, .	,, = 22·9
,, 60 ,, .	,, = 22·7	,, 36 ,, .	,, = 22·9
	Calculated for $C_6H_8O_7$.	,, 40 ,, .	,, = 22·8
		,, 88 ,, .	,, = 22·5
			Calculated for $C_6H_8O_7$.

Sohst and Tollens, *Lieb. Ann.* 245, 10, 12 (1888).

The other oxyacids and lactones exhibit similar phenomena.

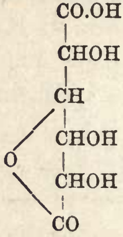
It may be mentioned that the higher rotatory power of the lactones compared with the acids is due to the former containing a closed ring, as, for instance, in :

Saccharic acid.



$$\begin{array}{l} \mathrm{CO.OH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CO.OH} \end{array}$$

Saccharic acid lactone.



As will be pointed out later (§ 25 *c*), the formation of a ring always increases the activity.

II. Connection between the Rotatory Power and the Chemical Composition of Carbon Compounds.

10. Optical Modifications. Pasteur's Investigations.—In 1815 Biot and Seebeck had observed that ordinary tartaric acid is dextrorotatory, and in 1842 Mitscherlich made the observation that racemic acid, which has the same constitution, is inactive; and, further, these two acids retained the same behaviour when converted into the crystallised sodium ammonium salts. Pasteur,[1] in 1848, found that when a solution of this double salt, prepared from racemic acid, was allowed to evaporate at a low temperature, hemihedral rhombic crystals separated out, which, like the salt prepared from dextrotartaric acid, had the formula $Na.NH_4.C_4H_4O_6 + 4H_2O$. All the crystals which separated out were not crystallographically identical, but could be divided into two groups. The crystals of these two groups differed by having, in the one, a hemihedral facet lying on the right of an edge where two faces meet, and in the other the same facet to the left of the same edge. The two kinds of crystals were enantiomorphic (v. § 2). The same phenomenon was later observed with other substances by Pasteur, who propounded the doctrine that *optically active carbon compounds, in general, possess the property of being able to crystallise in enantiomorphic forms.* In every case in which it has been possible to determine accurately the symmetry of the crystals, this has been confirmed.[1]

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[1] Pasteur, *C. r.* **26**, 535; **27**, 367 (1848); *Ann. chim. phys.* [3] **24**, 442 (1848).

When the two kinds of crystals had been mechanically separated, Pasteur found that solutions of the same concentration of each, when polarimetrically examined, showed exactly the same degree of rotation; but one solution was dextro-, the other lævorotatory. By mixing equal volumes of the solutions (of the same concentrations), an inactive liquid was produced. From the two sodium ammonium salts, *d*- and *l*-tartaric acids were obtained, and these also proved to be enantiomorphic.

Thus it was proved for the first time that an active substance can occur in two oppositely rotating modifications (optical antipodes); and, further, that equimolecular quantities of these may combine to an inactive compound (racemic modification), which can again be split up into its active components.

Besides the method of decomposing the racemic form by crystallisation, Pasteur discovered two others (v. § 15); and by means of these it has since been possible to obtain the active isomers from a very large number of racemates.

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[1] [See discussion on this question: Walden, *Ber.* **29**, 1692 (1896) **30**, 98 (1897); H. Traube, *Ber.* **29**, 2446; **30**, 288.]

Pasteur[1] discovered also a fourth optical modification of tartaric acid, which is formed when *d*- or *l*-tartrate of cinchonine is heated for some hours at 170°. The tartaric acid of the salt is converted to a large extent into racemic acid, but a part of it is transformed into an isomeric acid—mesotartaric acid—which is also inactive. This isomer is characterised by not being separable into *d*- and *l*-tartaric acids. Modifications of this nature are only possible, as was afterwards recognised, in the case of compounds which consist of two absolutely identical groups of atoms. If the two halves possess opposite rotatory powers, an inner compensation in the molecule takes place, and on this account the terms *constitutionally* or *configurationally inactive isomers* are applied to such compounds.

The oppositely disposed asymmetrical structure which the two enantiomorphic crystals of sodium ammonium tartrate possess, is exhibited in the aqueous solutions by optical dextro- and lævorotation due to the single molecules of the substance. This led Pasteur to the view that single molecules—like all material objects—may be divided into two classes, according to their shape and the repetition of their symmetrical parts: 1. Those whose mirror-image is superposable on themselves (straight flights of steps, cubes). 2. Those which are not superposable by their mirror-images (winding stairs, irregular tetrahedra, right- and left-handed screws, the right and the left hand). The molecules belonging to the first class possess a symmetrical structure; those of the second have their atoms asymmetrically arranged, and accordingly should exhibit optical activity.

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[1] Pasteur, *C. r.* **37**, 162 (1853).

With regard to racemic acid and the two active tartaric acids, Pasteur[1] says: 'Are the atoms of the dextro-acid grouped in the form of a right-handed helix, or do they stand at the corners of an irregular tetrahedron, or are they arranged in some other asymmetrical manner? We are not yet in a position to answer these questions. There can, however, be no doubt that an asymmetrical grouping after the manner of non-superposable mirror-images must be present. And we may be certain that the atoms of the lævo-acid have the reverse arrangement. Lastly, we know that racemic acid is produced by the union of these two reverse asymmetrical groupings of atoms.'

By these observations Pasteur introduced into science a new conception—that of *molecular asymmetry*. Before this novel idea bore much fruit, a great development of organic chemistry was necessary; and only after the constitutional formulæ of a very large number of carbon compounds had been determined, was it possible to investigate the connection between the atomic structure of the molecule and the optical activity.

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[1] Pasteur, 'Recherches sur la dissymétrie moléculaire des produits organiques naturels.' *Soc. chim. de Paris, Leçons de chimie professées en* 1860. German translation by M. and A. Ladenburg, *Ostwald's Classiker der exacten Wissenschaften*, No. 28.

11. The van't Hoff and Le Bel Theory.—One of the most important steps in the progress of our knowledge of the optical rotatory power was brought forward in 1874. In that year J. H. van't Hoff,[1] then in Utrecht, and a few weeks later J. A. Le Bel,[2] in Paris, showed that the occurrence of optical activity in carbon compounds stands in a certain relationship with the chemical structure. The fundamental idea, to which van't Hoff was led by the assumption of the tetrahedral solid angle positions of the atoms, and Le Bel by Pasteur's ideas on molecular asymmetry, has by later experience found a brilliant confirmation; and the further development of the theory, especially of the views on the position of the atoms in space, has called into existence a new branch of science—stereochemistry.

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[1] The paper was first published under the title, 'Voorstel tot uitbreiding der tegenwoordig in de scheikunde gebruikte structurformules in de ruimte; benevens en daarmeê samenhangende opmerking omtrent het verband tusschen optisch actief vermogen en chemische constitutie van organische verbindingen.' Utrecht 1874. At the end it is signed: 5 Sept. 1874, J. H. van't Hoff. An abstract of this paper appeared in 1875 in *Bull.* [2], **23**. There afterwards appeared: (1) *La chimie dans l'espace*, by J. H. van't Hoff. (Rotterdam 1875); (2) *Die Lagerung der Atome im Raume*, German translation of the former by Dr. F. Herrmann (Brunswick, 1877); (3) *Dix années dans l'histoire d'une théorie*, by J. H. van't Hoff (Rotterdam, 1887) [English translation: *Chemistry in Space*, by Marsh, 1891]; (4) *Stereochemie*, by W. Meyerhoffer, founded on van't Hoff's *Dix années*, &c. (Leipsic and Vienna, 1892); (5) *Die Lagerung der Atome im Raume*, by J. H. van't Hoff. 2nd edition. (Brunswick, 1894.)

[2] First publication, 'Sur les relations qui existent entre les formules atomiques des corps organiques et le pouvoir rotatoire de leurs dissolutions.' *Bull.* [2] **22**, 337, November number, 1874. Later papers in: *Bull.* [2] **23**, 338 (1875); **25**, 546 (1876); **27**, 444 (1877); **33**, 106 (1880); **37**, 300 (1882); [3] **7**, 164; **8**, 613 (1892). *C. r.* **89**, 312 (1879); **92**, 843 (1881); **110**, 144 (1890); **112**, 724 (1891); **114**, 304, 417 (1892).

The fundamentals of the theory are as follows :

1. If we imagine in a compound of the type CR_4 the carbon atom at the centre, and the four atoms (or radicles), with which it is united, at the four corners of a tetrahedron ; then, if these four atoms (or radicles) are all different, the resulting space formula ($CR_1R_2R_3R_4$) does not possess a plane of symmetry, and accordingly must be able to occur in two non-superposable forms, one of which is the mirror-image of the other. According to this view every compound which contains a so-called *asymmetric carbon atom* —*i.e.* one which is united with four different atoms or radicles, must be optically active and occur in a dextro-rotating and an equally strong lævo-rotating form.

To this experience has added that equal quantities of the two modifications are able to combine to form an inactive compound (racemate), which by certain means may be split up again into its active components.

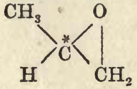
Asymmetric carbon atoms (*C) may occur in simple methane derivatives and in ordinary chained molecules; in benzene derivatives they can only occur in the side-chain, but in the hydrides of cyclic compounds they may also be present in the ring. Examples :

Ethylidene lactic acid .	$CH_3-{}^*CH.OH-COOH$
Mandelic acid . . .	$C_6H_5-{}^*CH.OH-COOH$

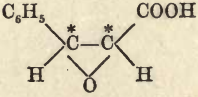
Cystine	$CH_3-*C(SH)(NH_2)-COOH$
Malic acid . . .	$COOH-*CH.OH-CH_2-COOH$
Tartaric acid . . .	$COOH-*CH.OH-*CH.OH-COOH$
Pentoses	$CH_2OH-*CH.OH-*CH.OH$ $-*CH.OH-CHO.$

Some other cases may be mentioned, from which it will be seen that of the four radicles two may be united together (propylene oxide), or one of them may be linked to two different asymmetric carbon atoms (phenoxyacrylic acid); and, further, that the asymmetry of a carbon atom may be conditioned by a group of atoms not directly connected with it (limonene, menthene):

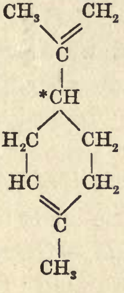
Propylene oxide



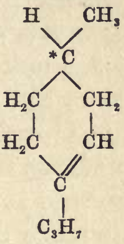
Phenoxyacrylic acid



Limonene



Menthene



2. In the case of compounds with two asymmetric carbon atoms, the molecule of which, like that of tartaric acid, consists of two similar halves, there must occur, according as the two halves possess the same or opposite rotatory powers, besides the dextro- and the lævo- active modifications, a third, which is inactive by intramolecular compensation, and not decomposable into active constituents. An inactive

modification of this nature is no longer possible if the molecule is not built up of two similar parts; but in this case four active isomers must be possible—two pairs of equal but opposite rotatory power. If the compound contain several asymmetric carbon atoms, a large number of active modifications of various rotatory powers, but occurring in pairs (antipodes), are possible, as well as a certain number of isomers inactive by compensation.

The number of possible isomers can be calculated if the structural formula of the compound is known, as will be shown in the following section.

With the *ethylene derivatives* with four dissimilar radicles $R_1R_2C=CR_3R_4$, all the atom-groups must lie in one plane if we imagine the two carbon-tetrahedra united along an edge of each, and no asymmetry can occur. Indeed, every ethylene compound has proved to be inactive[1] even when it has been produced from an active substance, as, for instance, fumaric and maleic acids from tartaric acid, bromocinnamic acid $C_6H_5-CBr=CH-COOH$ from cinnamic acid dibromide $C_6H_5-{}^*CHBr-{}^*CHBr-COOH$. Asymmetry is also impossible when an even number of doubly linked carbon atoms is added on to the type $R_1R_2C=CR_3R_4$. On the other hand, asymmetry, and consequently optical rotation, may occur, as van't Hoff[1] observes, when an odd number of carbon atoms is introduced, for then the four radicles no longer lie in one plane, but take up positions resembling those on the tetrahedral form. The simplest compounds of this nature would be the allene derivatives; observations on such are still wanting.

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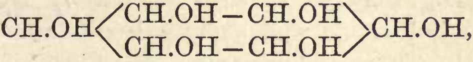
[1] Le Bel, *Bull.* [3] **8**, 613 (1892), regarded the activity of unsaturated compounds as possible, and Perkin, *J. C. S.* **53**, 695 (1888), believed that he had discovered it in the case of chlorofumaric and chloromaleic acid $COOH-CCl=CH-COOH$. Walden, *Ber.* **26**, 210 (1893), showed the fallacy of this observation.

Ring-compounds offer cases of asymmetry which can be foreseen (van't Hoff[2]). The simplest compounds would be the derivatives of tri- and tetramethylene, but no active compounds belonging to this class are yet known. We know, however, many active compounds derived from six-membered rings —namely, di-, tetra-, and hexa-hydrides of benzene. In the case of inositol,[3] which belongs to the last class:



$$CH.OH\left\langle\begin{matrix}CH.OH-CH.OH\\CH.OH-CH.OH\end{matrix}\right\rangle CH.OH,$$

it is not evident from the formula that an asymmetric carbon atom is present, and the asymmetry with the mirror-image form only appears when the positions of the H and OH on the two sides of the plane of the carbon ring are considered (cis- and trans-isomerism). Lastly, the derivatives (non-hydrides) of benzene may contain asymmetric carbon atoms in the side-chain.

The confirmation of the theory of van't Hoff and Le Bel has gradually been worked out in a most convincing manner. It has invariably been found that active compounds contain at least one asymmetric carbon atom, and where no such atom is present the compound is inactive. It has been shown that for substances with no asymmetric carbon atom for which a rotatory power was claimed—N-propyl alcohol, styrene, β-picoline, &c.—this claim is not well-founded. By direct experiment it has been proved that the rotatory power appears or vanishes with the production or annihilation of the asymmetric carbon atom. Thus Le Bel[1] transformed active amyl iodide, $CH_3.H.{}^*C.C_2H_5.CH_2I$, into inactive methyl-diethyl-methane, $CH_3.H.C.C_2H_5.C_2H_5$; Just,[2] by means of zinc and hydrochloric acid, produced from the same amyl iodide inactive dimethyl-ethyl-methane, $CH_3.H.C.C_2H_5.CH_3$; but by treating it with ethyl iodide and sodium he obtained active methyl-ethyl-propyl-methane, $CH_3.H.{}^*C.C_2H_5.C_3H_7$, and by warming with sodium active diamyl,

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[1] Van't Hoff, *Die Lagerung der Atome im Raume*, 2nd edition, 1894, pp. 68 to 76.

[2] *Ibid.* pp. 83, 84.

[3] See Bouveault, *Bull.* [3], 11, 144 (1894).

$$C_2H_5.CH_3.H.{}^*C-CH_2-CH_2-{}^*C.H.CH_3.C_2H_5.$$

These investigations led to the conclusion that for the appearance of activity the nature of the four radicles united with the asymmetric carbon atom is a matter of indifference. It had formerly been observed that on the introduction of a halogen into the active compound, the activity frequently disappeared; thus from lævorotatory malic acid inactive monobromosuccinic acid was obtained, from *l*-

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[1] Le Bel, *Bull.* [2], **25**, 546 (1876).

[2] Just, *Lieb. Ann.* **220**, 146 (1883).

mandelic acid inactive phenylbromacetic acid, and from *d*- and *l*- isopropylphenylglycollic acid inactive isopropylphenylchloracetic acid. It was afterwards discovered that the cause of the inactivity of these products was the formation of racemic compounds at the high temperature at which the reactions were carried out. If the temperature be kept low, then the halogen-products are also active. This was specially shown by Walden,[1] who prepared active chlorosuccinic acid by the action of phosphorus pentachloride on a chloroform solution of malic acid. He afterwards obtained a large number of active halogen-compounds, such as chloropropionic methyl ester, bromomalic ethyl ester, and phenylchloracetic acid, from *d*-ethylidene lactic acid, ethyl tartrate, and mandelic acid. Lastly, an explanation was given of the fact that numerous compounds exist which contain asymmetric carbon atoms and yet are inactive. Some were proved to be of the racemic type by resolution into their active components ; the inactivity of others, such as mesotartaric acid, dulcitol, mucic acid, which are constituted of two similar parts, was recognised as due to the opposite rotatory power of the two halves of the molecule. In a third series of asymmetric compounds it was found that they possess such a low rotatory power that an exceedingly thick layer must be examined, or the addition of certain substances (such as boric acid) is required, in order to render it recognisable. Thus in every case the views expressed by van't Hoff and Le Bel have been in thorough agreement with experimental evidence, and in cases where any difference appeared, this has been removed by later investigation. We may regard the doctrine of the asymmetric carbon atom as one of the best-founded of the theories in chemistry.

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[1] Walden, *Ber.* **26**, 214 (1893) ; **28**, 1287 (1895). See also Le Bel, *Bull.* [3], **9**, 674 (1893), and *Ber.* **28**, 1923. Walden's reply: *Ber.* **28**, 2766.

Asymmetric Nitrogen.—Compounds of trivalent nitrogen with three different radicles seem always to be inactive. All attempts to split up the tartrates of ethylbenzylamine, benzylhydroxylamine, methylaniline, tetrahydroquinoline, and tetrahydropyridine have been unsuccessful. On the other hand, an active derivative of pentavalent nitrogen has been obtained—namely, methyl-ethyl-propyl-isobutylammonium chloride. Le Bel[1] was able by means of a fungus-culture to decompose the prepared inactive salt, and obtained the lævorotatory chloride ($[a]_D = -7$ to 8°) which could be converted into the active chloroplatinate, chloromercurate, and acetate. The chloraurate has only a low lævorotation, and on addition of hydrochloric acid becomes dextrorotatory. The sulphate proved to be inactive.

Ammonium compounds which contain two similar radicles, such as the chlorides of dimethylethylpropyl-, methylethyldipropyl-, ethyldipropylisobutyl-, and ethylpropyldiisobutyl ammonium, cannot, as Le Bel found, be decomposed into an active form by a fungoid growth.

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[1] Le Bel, *C. r.* **112**, 724 (1891).

Further details on asymmetric nitrogen belong to stereochemistry rather than here.

12. Calculation of the Number of Optically Active Isomers of a Compound from the Number of Asymmetric Carbon Atoms which it contains. Already in 1875, van't Hoff, in his *Chimie dans l'espace*, gave the formulæ for the derivation of the possible number of isomers; but for a long time these obtained no experimental confirmation, and it is only comparatively recently, by the splendid work of E. Fischer on the sugars, that the correctness of the theoretical previsions has been absolutely proved. Our knowledge of other classes of compounds has also been increased, and now we are acquainted with the different optical modifications of more than 100 active substances.

If we divide the compounds which contain a chain of carbon atoms united by single bonds into the three classes given below, then the number of possible stereoisomers—optically active and inactive modifications—can be easily found.

n denotes the number of asymmetric carbon atoms contained in the molecule of the substance;

N denotes the total number of stereoisomers which may be divided into:

- **i** the inactive, non-decomposable modifications, and
- **a** the active forms, which occur in pairs (optical antipodes) of equal but opposite

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rotatory power. These active isomers lead to

$\mathbf{r} = \frac{\mathbf{a}}{2}$ inactive, decomposable racemic forms.

First class : **n**, even or odd.—Chemical structural formula not consisting of two equal parts.

If we denote by R and R_1 the radicles at the ends of the chain, and by *a* and *b* those united to the intermediary carbon atoms of the chain, then the type is :

$$R-(^*Cab)_{1,2,3....}-R_1\ ;$$

and as examples we may take :

Malic acid	$COOH-{}^*CH.OH-CH_2-COOH$
Phenyl-α-chlorolactic acid .	$C_6H_5-{}^*CH.OH-{}^*CH.Cl-COOH$
Pentoses	$CH_2.OH-{}^*CH.OH-{}^*CH.OH$ $-{}^*CH.OH-CHO$
Hexonic acids	$CH_2.OH-({}^*CH.OH)_4-COOH$

Compounds whose chain contains at any point a non-asymmetric carbon atom (CH_2, CCl_2, CO) also belong to this class, as, for instance :

Butylchloral-aldol . . .	$CH_3-{}^*CH.Cl-CCl_2-{}^*CH.OH$ $-{}^*CH(CHO)-{}^*CH.OH-CH_3$

In this case we have :

(I.) [1] $\mathbf{N=2^n}$, $\mathbf{a=\cancel{n}}$, N $\mathbf{i=0}$.

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[1] Expressions (I.) and (II.) were given by van't Hoff *La Chimie dans l'espace*, 1875, pp. 9–12). Expression (II. is often written in the forms :

$$N = 2^{\frac{n}{2}} + \frac{2^n - 2^{\frac{n}{2}}}{2},\ \text{or}\ 2^{\frac{n}{2}-1}(2^{\frac{n}{2}}+1),\ \text{or}\ \tfrac{1}{2}(2^n + 2^{\frac{n}{2}}).$$

E. Fischer (*Lieb. Ann.* **270**, 67, 1892) first called attention to expression (III.).

The following table gives a list of the number of possible isomers of compounds containing different numbers of asymmetric carbon atoms:

$n =$	1	2	3	4	5	6
$N = a =$	2	4	8	16	32	64
$r =$	1	2	4	8	16	32

Second class: n, even.—Chemical structure consists of two equal parts.

Type: $R-({}^*Cab)_{2,4,6\ldots}-R.$

Examples:

Tartaric acid . . .	$COOH-{}^*CH.OH-{}^*CH.OH-COOH$
Sym. dimethylsuccinic acid	$COOH-{}^*CH.CH_3-{}^*CH.CH_3-COOH$
Hydrobenzoin . . .	$C_6H_5-{}^*CH.OH-{}^*CH.OH-C_6H_5$
Hexitols	$CH_2OH-({}^*CH.OH)_4-CH_2OH$
Tetraoxy-dicarboxylic acid .	$COOH-({}^*CH.OH)_4-COOH$

Compounds whose structural formula consists of two similar parts, and which contain an even number of non-asymmetric carbon atoms in the middle, also belong to this group—*e.g.*:

Dimethyladipic acid	$COOH-{}^*CH.CH_3-CH_2-CH_2-{}^*CH.CH_3-CO$
Diallyl bromide	$CH_2Br-{}^*CH.Br-CH_2-CH_2-{}^*CH.Br-CH_2Br$

In this case:

(II.) $$N=2^{n-1}+2^{\frac{n}{2}-1},$$

$$a=2^{n-1}, \qquad i=2^{\frac{n}{2}-1},$$

$n=$	2	4	6	8
N =	3	10	36	136
$a=$	2	8	32	128
$i=$	1	2	4	8
$r=$	1	4	16	64

Third class: n, odd.—Chemical structural formula consists of two equal parts united by a middle carbon atom.

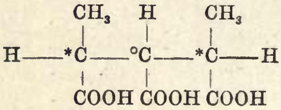
Type: $R-({}^*Cab)_{3,5,7....}-R.$

Examples:

Trioxyglutaric acids
$COOH-{}^*CH.OH-{}^\circ CH.OH-{}^*CH.OH-COOH$

α-Glucoheptitol
$CH_2OH-{}^*CH.OH-{}^*CH.OH-{}^\circ CH.OH-{}^*CH.OH$
$-{}^*CH.OH-CH_2OH$

Dimethyltricarballylic acid . .



$$\begin{array}{ccccccccc} & & CH_3 & & H & & CH_3 & & \\ & & | & & | & & | & & \\ H & — & {}^*C & — & {}^\circ C & — & {}^*C & — & H \\ & & | & & | & & | & & \\ & & COOH & & COOH & & COOH & & \end{array}$$

In these cases the middle carbon atom of the chain is:

asymmetric (active), when the two equal parts of the chain to which it is united are asymmetric in the same direction—*i.e.* when they possess the same direction of rotation;

symmetric (inactive), when the two equal parts of the chain are asymmetric in opposite directions—*i.e.* when their rotations annul each other.

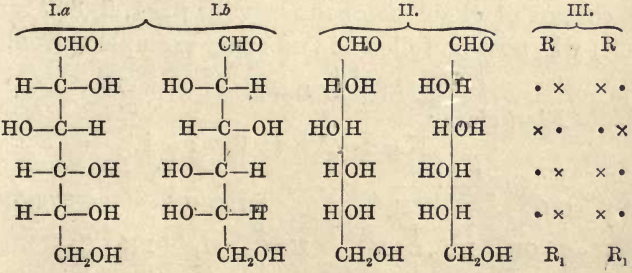
In both cases we have the following expressions for the number of isomers, the middle carbon atom (°C) being included in n:

(III.) $$N=2^{n-1},$$

$$a=2^{n-1}-2^{\frac{n-1}{2}}, \qquad i=2^{\frac{n-1}{2}}.$$

$n=$	3	5	7	9
$N=$	4	16	64	256
$a=$	2	12	56	240
$i=$	2	4	8	16
$r=$	1	6	28	120

For the derivation of the several stereoisomers of a compound the method of representation suggested by E. Fischer[1] can best be used. This method consists in projecting on to the plane of the paper the model of the configuration of the molecule (using the well-known carbon atom models), so that all the carbon atoms lie in a straight line, and the radicles (H and OH) united to these are represented to the right and to the left. The projection of *d*-glucose is given in I.*a*, whilst its mirror-image I.*b* represents *l*-glucose. The method of writing these can be contracted to II., or, if we set H= • and OH= ×, we obtain the short form III.



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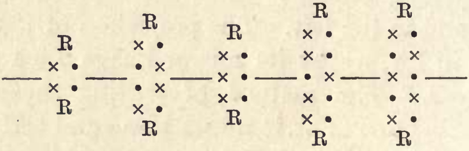
[1] E. Fischer, *Ber.* 24, 2683 (1891).

In the following configurational formulæ the inactive, non-decomposable modifications can easily be recognised by their being divisible by a horizontal line into two similar halves, one of which is the mirror-image of the other. The compensation of the two rotatory effects which takes place within the molecule is by this means clearly expressed, for if we lay the four radicles in diagram 1 (under) on a spiral in the order $\overset{1}{\cdot}\overset{2}{\times}\overset{3}{R}(\cdot\overset{4}{\times}R)$, then the upper half will form a right-handed, and the lower a left-handed screw. If the compound contains an odd number of carbon atoms, then the bisecting line passes through the middle (non-asymmetric) one. The following diagrams represent inactive compounds:



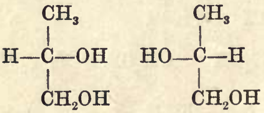
The derivation of the possible optical modifications of chain compounds with $n=1, 2, 3, 4$, and 5, will now be followed and some examples given.

I. $n=1$.

First class:

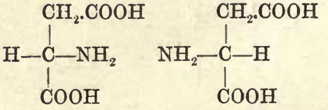
$$N=a=2, \quad i=0, \quad r=1.$$

Examples:



$$\underbrace{\begin{array}{c} CH_3 \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array} \quad \begin{array}{c} CH_3 \\ | \\ HO-C-H \\ | \\ CH_2OH \end{array}}$$

Dextro- and lævo-propylene glycol



$$\underbrace{\begin{array}{c} CH_2.COOH \\ | \\ H-C-NH_2 \\ | \\ COOH \end{array} \quad \begin{array}{c} CH_2.COOH \\ | \\ NH_2-C-H \\ | \\ COOH \end{array}}$$

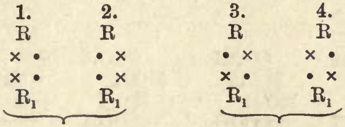
Dextro- and lævo-aspartic acid

II. n=2.

A. *First class :*

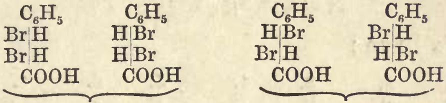
$$N = a = 4, \quad i = 0, \quad r = 2.$$

Four active combinations are possible ; two pairs of antipodes :



$$\underbrace{\begin{array}{cc}1. & 2.\\ R & R\\ \times\ \bullet & \bullet\ \times\\ \times\ \bullet & \bullet\ \times\\ R_1 & R_1\end{array}} \qquad \underbrace{\begin{array}{cc}3. & 4.\\ R & R\\ \bullet\ \times & \times\ \bullet\\ \times\ \bullet & \bullet\ \times\\ R_1 & R_1\end{array}}$$

Cinnamic acid dibromide offers an example of this, and we know the four active and the two racemic forms :



$$\underbrace{\begin{array}{cc}C_6H_5 & C_6H_5\\ Br \mid H & H \mid Br\\ Br \mid H & H \mid Br\\ COOH & COOH\end{array}} \qquad \underbrace{\begin{array}{cc}C_6H_5 & C_6H_5\\ H \mid Br & Br \mid H\\ Br \mid H & H \mid Br\\ COOH & COOH\end{array}}$$

Which of these configurations belongs to each isomer has not yet been determined.

Other examples are :

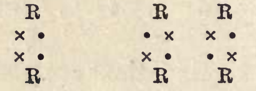
Phenyl-α-chlorolactic acid	$C_6H_5 - CH.OH - CH.Cl - COOH$
Phenyl-β-chlorolactic acid	$C_6H_5 - CH.Cl - CH.OH - COOH$
Trioxybutyric acid	$CH_2OH - CH.OH - CH.OH - COOH$

B. *Second class :*

$$N = 3, \quad a = 2, \quad i = 1, \quad r = 1.$$

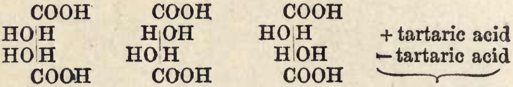
If $R = R_1$ then, of the combinations given under

A, 1 and 2 are identical, as can be seen by turning one of them upside down, and there remain:



inactive oppositely active

Example:



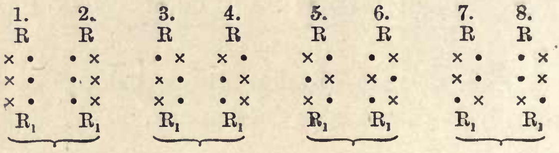
Mesotartaric acid Dextrotartaric acid Lævotartaric acid Racemic acid

III. n=3.

A. *First class:*

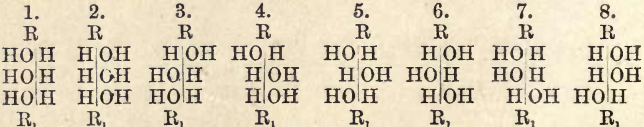
$$N=a=8, \quad i=0, \quad r=4.$$

We have:



Examples:

	R_1		R
Pentoses	$CH_2OH - (CH.OH)_3 - CHO$
Pentonic acids . . .	$CH_2OH - (CH.OH)_3 - COOH$



l-ribose *l*-ribonic acid; unknown; *l*-arabinose *l*-arabonic acid; *d*-arabinose; unknown; *l*-xylose *l*-xylonic acid; Lyxose Lyxonic acid; unknown

B. *Third class :*

$$N=4, \quad a=2, \quad i=2, \quad r=1.$$

In the configurations given under A, the following are identical when $R=R_1$:

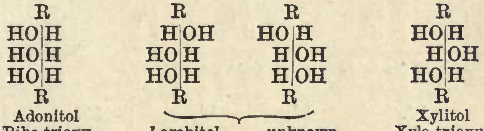
1 with 2	4 with 7
3 „ 8	5 „ 6

and there remain :

1.	3.	4.	5.
R	R	R	R
× •	• ×	× •	× •
× •	× •	• ×	• ×
× •	× •	• ×	× •
R	R	R	R
inactive	oppositely active		inactive

Examples :

Pentitols . . . . $CH_2OH—(CH.OH)_3—CH_2OH$
Trioxyglutaric acids . . $COOH—(CH.OH)_3—COOH$



Adonitol
Ribo-trioxy-glutaric acid
inactive

l-arabitol
l-trioxyglutaric acid

unknown

Xylitol
Xylo-trioxy-glutaric acid
inactive

IV. n=4.

A. *First class :*

$$N=a=16, \quad i=0, \quad r=8.$$

1.	2.	3.	4.	5.	6.	7.	8.
R	R	R	R	R	R	R	R
× •	• ×	• ×	× •	× •	• ×	× •	• ×
× •	• ×	× •	• ×	• ×	× •	× •	• ×
× •	• ×	× •	• ×	× •	• ×	• ×	× •
× •	• ×	× •	• ×	× •	• ×	× •	• ×
R_1	R_1	R_1	R_1	R_1	R_1	R_1	R_1

$$\underbrace{\begin{array}{cc} 9. & 10. \\ R & R \\ \times\ \bullet & \bullet\ \times \\ \times\ \bullet & \bullet\ \times \\ \times\ \bullet & \bullet\ \times \\ \bullet\ \times & \times\ \bullet \\ R_1 & R_1 \end{array}} \qquad \underbrace{\begin{array}{cc} 11. & 12. \\ R & R \\ \bullet\ \times & \times\ \bullet \\ \bullet\ \times & \times\ \bullet \\ \times\ \bullet & \bullet\ \times \\ \times\ \bullet & \bullet\ \times \\ R_1 & R_1 \end{array}} \qquad \underbrace{\begin{array}{cc} 13. & 14. \\ R & R \\ \bullet\ \times & \times\ \bullet \\ \times\ \bullet & \bullet\ \times \\ \bullet\ \times & \times\ \bullet \\ \times\ \bullet & \bullet\ \times \\ R_1 & R_1 \end{array}} \qquad \underbrace{\begin{array}{cc} 15. & 16. \\ R & R \\ \bullet\ \times & \times\ \bullet \\ \times\ \bullet & \bullet\ \times \\ \times\ \bullet & \bullet\ \times \\ \bullet\ \times & \times\ \bullet \\ R_1 & R_1 \end{array}}$$

Of the

hexoses . . . . $\overset{R_1}{CH_2OH}—(CH.OH)_4—\overset{R}{CHO}$
and hexonic acids . . . $CH_2OH—(CH.OH)_4—COOH$

the following of these sixteen active configurations are known :

$$\underbrace{\begin{array}{cc} 5. & 6. \\ R & R \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ R_1 & R_1 \\ l & d \end{array}}_{\text{Glucose, gluconic acid.}} \qquad \underbrace{\begin{array}{cc} 7. & 8. \\ R & R \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ R_1 & R_1 \\ d & l \end{array}}_{\text{Gulose, gulonic acid.}} \qquad \begin{array}{c} 9. \\ R \\ \mathrm{HO|H} \\ \mathrm{HO|H} \\ \mathrm{HO|H} \\ \mathrm{H|OH} \\ R_1 \\ d \\ \text{Talose, talonic acid.} \end{array}$$

$$\underbrace{\begin{array}{cc} 11. & 12. \\ R & R \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ R_1 & R_1 \\ l & d \end{array}}_{\text{Mannose, mannonic acid.}} \qquad \underbrace{\begin{array}{cc} 13. & 14. \\ R & R \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ R_1 & R_1 \\ d & l \end{array}}_{\text{Idose, idonic acid.}} \qquad \underbrace{\begin{array}{cc} 15. & 16. \\ R & R \\ \mathrm{H|OH} & \mathrm{HO|H} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{HO|H} & \mathrm{H|OH} \\ \mathrm{H|OH} & \mathrm{HO|H} \\ R_1 & R_1 \\ d & l \end{array}}_{\text{Galactose, galactonic acid.}}$$

B. *Second class :*

$$N=10, \quad a=8, \quad i=2, \quad r=4.$$

This number of isomers can be ascertained by setting $R=R_1$ in the configurations given under A, and we find that the following become identical:

1 with 2 5 with 8
3 „ 10 6 „ 7
4 „ 9 15 „ 16

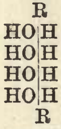
so that there remain:

$$1-(3,4)-(5,6)-(11,12)-(13,14)-15.$$

The hexitols	$CH_2OH-(CH.OH)_4-CH_2OH$
and saccharic acids . .	$COOH-(CH.OH)_4-COOH$

belong to this group, and of the latter all the ten forms are known:

1.

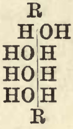


$$\begin{array}{c} R \\ \begin{array}{r|l} HO & H \\ HO & H \\ HO & H \\ HO & H \end{array} \\ R \end{array}$$

inactive

Allomucic acid

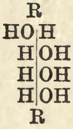
3.



$$\begin{array}{c} R \\ \begin{array}{r|l} H & OH \\ HO & H \\ HO & H \\ HO & H \end{array} \\ R \end{array}$$

l

4.

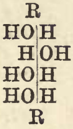


$$\begin{array}{c} R \\ \begin{array}{r|l} HO & H \\ H & OH \\ H & OH \\ H & OH \end{array} \\ R \end{array}$$

d

Talitol
Talomucic acid

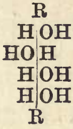
5.



$$\begin{array}{c} R \\ \begin{array}{r|l} HO & H \\ H & OH \\ HO & H \\ HO & H \end{array} \\ R \end{array}$$

l

6.

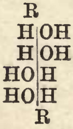


$$\begin{array}{c} R \\ \begin{array}{r|l} H & OH \\ HO & H \\ H & OH \\ H & OH \end{array} \\ R \end{array}$$

d

Sorbitol
Saccharic acid

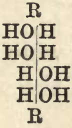
11.



$$\begin{array}{c} R \\ \begin{array}{r|l} H & OH \\ H & OH \\ HO & H \\ HO & H \end{array} \\ R \end{array}$$

l

12.

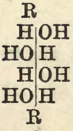


$$\begin{array}{c} R \\ \begin{array}{r|l} HO & H \\ HO & H \\ H & OH \\ H & OH \end{array} \\ R \end{array}$$

d

Mannitol
Mannosaccharic acid

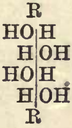
13.



$$\begin{array}{c} R \\ \begin{array}{r|l} H & OH \\ HO & H \\ H & OH \\ HO & H \end{array} \\ R \end{array}$$

d

14.

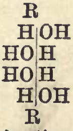


$$\begin{array}{c} R \\ \begin{array}{r|l} HO & H \\ H & OH \\ HO & H \\ H & OH \end{array} \\ R \end{array}$$

l

Iditol
Idosaccharic acid

15.



$$\begin{array}{c} R \\ \begin{array}{r|l} H & OH \\ HO & H \\ HO & H \\ H & OH \end{array} \\ R \end{array}$$

inactive
Dulcitol
Mucic acid

V. n=5.

A. *First class:*

$$N=a=32, \quad i=0, \quad r=16.$$

Omitting R and R_1, the following are the thirty-two possible combinations:

1.	2.	3.	4.	5.	6.	7.	8.
× •	• ×	• ×	× •	× •	• ×	× •	• ×
× •	• ×	× •	• ×	• ×	× •	× •	• ×
× •	• ×	× •	• ×	× •	• ×	• ×	× •
× •	• ×	× •	• ×	× •	• ×	× •	• ×
× •	• ×	× •	• ×	× •	• ×	× •	• ×

9.	10.	11.	12.	13.	14.	15.	16.
× •	• ×	× •	• ×	• ×	× •	• ×	× •
× •	• ×	× •	• ×	• ×	× •	× •	• ×
× •	• ×	× •	• ×	× •	• ×	• ×	× •
• ×	× •	× •	• ×	× •	• ×	× •	• ×
× •	• ×	• ×	× •	× •	• ×	× •	• ×

17.	18.	19.	20.	21.	22.	23.	24.
• ×	× •	• ×	× •	× •	• ×	× •	• ×
× •	• ×	× •	• ×	• ×	× •	• ×	× •
× •	• ×	× •	• ×	• ×	× •	× •	• ×
• ×	× •	× •	• ×	× •	• ×	• ×	× •
× •	• ×	• ×	× •	× •	• ×	× •	• ×

25.	26.	27.	28.	29.	30.	31.	32.
× •	• ×	× •	• ×	× •	• ×	× •	• ×
• ×	× •	× •	• ×	× •	• ×	× •	• ×
× •	• ×	• ×	× •	• ×	× •	× •	• ×
× •	• ×	• ×	× •	× •	• ×	• ×	× •
• ×	× •	× •	• ×	• ×	× •	• ×	× •

Only few substances are known which correspond to any of these configurations, and these are:

8.	8.	16.	16.
CHO	COOH	CHO	COOH
H | OH	H | OH	HO | H	HO | H
H | OH	H | OH	H | OH	H | OH
HO | H	HO | H	HO | H	HO | H
H | OH	H | OH	H | OH	H | OH
H | OH	H | OH	H | OH	H | OH
CH_2OH	CH_2OH	CH_2OH	CH_2OH
α-glucoheptose	α-glucoheptonic acid	β-glucoheptose	β-glucoheptonic acid

B. *Third class :*

$$N=16, \quad a=12, \quad i=4, \quad r=6.$$

When $R=R_1$, then, of the configurations given under A, the following are identical :

1	with	2	13	with	32	18	with	25
3	,,	12	14	,,	31	19	,,	20
4	,,	11	15	,,	30	21	,,	28
5	,,	10	16	,,	29	22	,,	27
6	,,	9	17	,,	26	23	,,	24
7	,,	8						

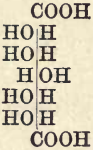
As the formula for the calculation of the number of possible isomers indicates, there are sixteen configurations left; namely, six active pairs and four inactive forms. These are :

1.	3.	4.	5.	6.	7.	13.	14.
× •	• ×	× •	× •	• ×	× •	• ×	× •
× •	× •	• ×	• ×	× •	× •	• ×	× •
× •	× •	• ×	× •	• ×	• ×	× •	• ×
× •	× •	• ×	× •	• ×	× •	× •	• ×
× •	× •	• ×	× •	• ×	× •	× •	• ×
inactive	active		active		inactive	active	

15.	16.	17.	18.	19.	21.	22.	23.
• ×	× •	• ×	× •	• ×	× •	• ×	× •
× •	• ×	× •	• ×	× •	• ×	× •	• ×
• ×	× •	× •	• ×	× •	• ×	× •	× •
× •	• ×	• ×	× •	× •	× •	• ×	• ×
× •	• ×	× •	• ×	• ×	× •	• ×	× •
active		active		inactive	active		inactive

Of these configurations the following have been determined ;

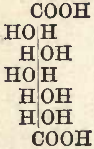
7.



$$\begin{array}{r|l} \multicolumn{2}{c}{\text{COOH}} \\ \text{HO} & \text{H} \\ \text{HO} & \text{H} \\ \text{H} & \text{OH} \\ \text{HO} & \text{H} \\ \text{HO} & \text{H} \\ \multicolumn{2}{c}{\text{COOH}} \end{array}$$

α-glucopentoxypimelic acid
(from α-glucoheptose).

16.



$$\begin{array}{r|l} \multicolumn{2}{c}{\text{COOH}} \\ \text{HO} & \text{H} \\ \text{H} & \text{OH} \\ \text{HO} & \text{H} \\ \text{H} & \text{OH} \\ \text{H} & \text{OH} \\ \multicolumn{2}{c}{\text{COOH}} \end{array}$$

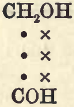
β-glucopentoxypimelic acid
(from β-glucoheptose).

[Fischer, *Lieb. Ann.* **270**, 89 and 91 (1892).]

[The method by which the orientation of the H and OH groups in the sugars has been carried out by E. Fischer can best be indicated by an example.

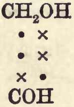
Arabinose is a pentose which occurs in the *d*-, *l*-, and *r*- forms. The possible configurations which it may have are:

I.



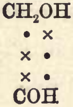
$$\begin{array}{c} \text{CH}_2\text{OH} \\ \bullet\ \times \\ \bullet\ \times \\ \bullet\ \times \\ \text{COH} \end{array}$$

II.



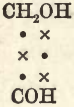
$$\begin{array}{c} \text{CH}_2\text{OH} \\ \bullet\ \times \\ \bullet\ \times \\ \times\ \bullet \\ \text{COH} \end{array}$$

III.



$$\begin{array}{c} \text{CH}_2\text{OH} \\ \bullet\ \times \\ \times\ \bullet \\ \times\ \bullet \\ \text{COH} \end{array}$$

IV.

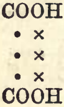


$$\begin{array}{c} \text{CH}_2\text{OH} \\ \bullet\ \times \\ \times\ \bullet \\ \bullet\ \times \\ \text{COH} \end{array}$$

along with the mirror-image form of each. Meantime we shall omit to consider these mirror-image forms, for it will suffice to establish one of these configurations for arabinose—that will be then either *d*- or *l*-arabinose and the mirror-image configuration will be the other one.

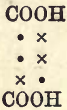
Arabinose on oxidation gives arabonic acid, which is active. This acid, which is trioxyglutaric acid, must have one of the following configurations:

V.



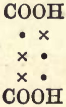
$$\begin{array}{c} \text{COOH} \\ \bullet\ \times \\ \bullet\ \times \\ \bullet\ \times \\ \text{COOH} \end{array}$$

VI.



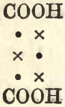
$$\begin{array}{c} \text{COOH} \\ \bullet\ \times \\ \bullet\ \times \\ \times\ \bullet \\ \text{COOH} \end{array}$$

VII.



$$\begin{array}{c} \text{COOH} \\ \bullet\ \times \\ \times\ \bullet \\ \times\ \bullet \\ \text{COOH} \end{array}$$

VIII.

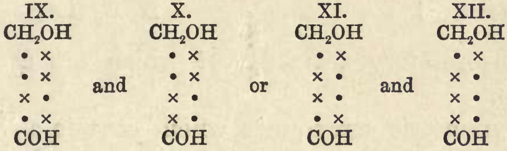


$$\begin{array}{c} \text{COOH} \\ \bullet\ \times \\ \times\ \bullet \\ \bullet\ \times \\ \text{COOH} \end{array}$$

and of these VI. and VII. are identical. As it is active it cannot have configuration V. nor VIII., both of which represent inactive molecules (see p. 66). VI. and VII. are derived from II. and III., therefore one of these latter must represent arabinose.

By adding on hydrocyanic acid to arabinose, then saponifying the nitrile and subsequently reducing the acid to aldehyde, glucose and mannose are produced.

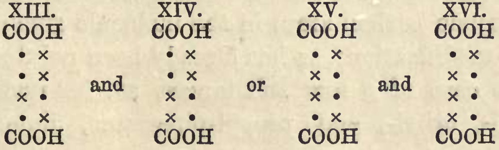
The configurations of glucose and mannose must, therefore, be:



$$\begin{array}{ccccccc}
\text{IX.} & & \text{X.} & & \text{XI.} & & \text{XII.}\\
CH_2OH & & CH_2OH & & CH_2OH & & CH_2OH\\
\bullet\ \times & & \bullet\ \times & & \bullet\ \times & & \bullet\ \times\\
\bullet\ \times & \text{and} & \bullet\ \times & \text{or} & \times\ \bullet & \text{and} & \times\ \bullet\\
\times\ \bullet & & \times\ \bullet & & \times\ \bullet & & \times\ \bullet\\
\bullet\ \times & & \times\ \bullet & & \bullet\ \times & & \times\ \bullet\\
COH & & COH & & COH & & COH
\end{array}$$

the first pair being derived from formula II., the second pair from III.

Glucose and mannose on oxidation yield saccharic acid and mannosaccharic acid, both of which are active. The configurations of these acids must be:

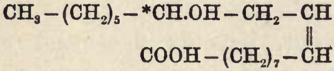


$$\begin{array}{ccccccc}
\text{XIII.} & & \text{XIV.} & & \text{XV.} & & \text{XVI.}\\
COOH & & COOH & & COOH & & COOH\\
\bullet\ \times & & \bullet\ \times & & \bullet\ \times & & \bullet\ \times\\
\bullet\ \times & \text{and} & \bullet\ \times & \text{or} & \times\ \bullet & \text{and} & \times\ \bullet\\
\times\ \bullet & & \times\ \bullet & & \times\ \bullet & & \times\ \bullet\\
\bullet\ \times & & \times\ \bullet & & \bullet\ \times & & \times\ \bullet\\
COOH & & COOH & & COOH & & COOH
\end{array}$$

Of these, however, XV. is inactive by internal compensation (see p. 66), consequently the pair of configurations XIII. and XIV. must apply to saccharic and mannosaccharic acids, IX. and X. to glucose and mannose, and II. to arabinose.]

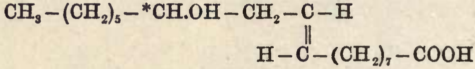
Asymmetric molecules of a chain form which contain *doubly linked* carbon atoms must yield the *d*- and *l*- modifications of both of the forms produced by cis-trans-isomerism. Walden,[1] who called attention to this point, suggests that the following may be compounds of this nature:

Dextrorotatory ricinoleic acid Cis-form



$$\begin{array}{r} CH_3-(CH_2)_5-{*}CH.OH-CH_2-CH \\ \| \\ COOH-(CH_2)_7-CH \end{array}$$

Dextrorotatory ricinelaïdic acid Trans-form



$$\begin{array}{l} CH_3-(CH_2)_5-{*}CH.OH-CH_2-C-H \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \| \\ \qquad\qquad\qquad\qquad\qquad\quad H-C-(CH_2)_7-COOH \end{array}$$

the lævorotatory antipodes of which are not yet known.

Asymmetric compounds which contain a *triple-bond* can only give one pair of optical antipodes: thus both the acids just mentioned yield the same *d*-ricinstearolic acid which has the formula:

$$CH_3-(CH_2)_5-{*}CH.OH-CH_2-C\equiv C-(CH_2)_7-COOH.$$

(Goldsobel.[2])

Ring compounds: Those which contain only one asymmetric carbon atom in the molecule give *d*-, *l*-, and *r*- modifications, as has already been pointed out in the case of a few substances, as, for instance, methyl-, ethyl-, and propyl-piperidine, limonene, menthene, camphene, pinene, &c.

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[1] Walden, *Ber.* **27**, 3476 (1894).

[2] Goldsobel, *Ber.* **27**, 3121 (1894).

Cyclic compounds with two asymmetric carbon atoms may occur in four active isomeric forms (two pairs of antipodes), and two racemic modifications. These six forms are known for the camphoric acids, of which there exist, according to Aschan,[1] only the following :—(1) The ordinary *d*-, *l*-, and *r*- camphoric acids, which are of the malenoid or cis-form, and (2) *d*-, *l*-, and *r*- isocamphoric acids, which are of the fumaroid or trans-type. The constitution of camphoric acid is not yet definitely settled, but the fact that these six, and only these six, forms are known to exist, supports the view that there are two asymmetric carbon atoms present.

The same points seem to apply to other cyclic compounds, as, for instance, borneol, the constitution of which, however, is also not known with certainty.

Further relationships between the optical modifications will be found in the section on the 'production of active isomers' (§ 17).

Physical and Chemical Behaviour of the Optical Modifications.

13. Properties of Racemic Substances.

(*a*) The *molecular weight* of a crystallisable racemic compound must be double that of the active antipodes, since its inactivity shows that it is constituted of two molecules of the latter. This has not yet been proved by the methods of molecular weight determination at present available. The cryoscopic method leads to the molecular weight of the active forms, which proves that in dilute solution the racemic compound is split up into its components. This has been proved for ordinary racemic acid, *r*-isonitrosolimonene, &c. Similarly, the vapour-density determination of diethyl racemate led to the molecular weight of the corresponding tartaric ester, which shows that volatile racemic compounds suffer dissociation on vaporisation.

---

[1] Aschan, *Ber.* 27, 2001 (1894).

(*b*) The *crystal form* of racemic compounds shows essential differences from those of the two active modifications. The latter always appear in two crystal forms which are enantiomorphic, but this is not the case with racemates. The racemates are only able to yield one sort of crystals, and these belong to such crystal-groups wherein no enantiomorphic forms are possible. The principal means of recognising true racemic compounds lies in this difference.

(*c*) In the *amount of water of crystallisation* which they contain, the racemates sometimes agree with and sometimes differ from the active forms; no general rule can be given in this connection.

As examples of the facts mentioned in (*b*) and (*c*), the following may be cited:

Racemic and tartaric acids:	Crystal-group.
Racem. $[C_4H_6O_6 + H_2O]_2$	triclinic-holohedral
Active $C_4H_6O_6$	monoclinic-hemimorphic
Sodium ammonium racemate and tartrate:	
Racem. $[Na.NH_4.C_4H_4O_6 + H_2O]_2$	monoclinic-holohedral
Active $Na.NH_4.C_4H_4O_6 + 4H_2O$	rhombic-hemihedral

Sodium racemate and tartrate:

Racem. $[Na_2.C_4H_4O_6+2H_2O]_2$	monoclinic-holohedral
Active $Na_2.C_4H_4O_6+2H_2O$	rhombic-hemihedral

Potassium antimonyl racemate and tartrate:

Racem. $[K.SbO.C_4H_4O_6+\frac{1}{2}H_2O]_2$	rhombic-holohedral
Active $K.SbO.C_4H_4O_6+\frac{1}{2}H_2O$	rhombic-hemihedral

Carvone tetrabromide:

Racem. $[C_{10}H_{14}Br_4O]_2$	monoclinic-holohedral
Active $C_{10}H_{14}Br_4O$	rhombic-hemihedral

(*d*) The *density* of crystallised racemates is generally found to be greater than that of the active forms; in some cases, however, it is smaller. One substance is known which has the same density in both forms.

Examples:

	Racemic Form.	Active Form.	R−A.
Tartaric (and racemic) acid—water free	1·788	1·759	+0·029
Malic acid	1·601	1·595	+0·006
Camphoric acid	1·228	1·188	+0·040
Limonene tetrabromide	2·225	2·134	+0·091
Carvoxime	1·126	1·108	+0·018
Bromosuccinic acid	2·073	2·093	−0·02
Glutaminic acid	1·511	1·538	−0·027
Mandelic acid	1·300	1·341	−0·041
Carvone tribromide	1·958	1·958	0

In those cases in which the densities of the two forms are not the same, we may be quite certain that the racemic form is a true chemical compound. The active isomers have the same density, and that of a mechanical mixture of them we should expect would be the same—since we know that in the case of isomorphous mixed-crystals the density is an additive property. As this is generally not the case with racemates, it points to a contraction or expansion having taken place in their production, which denotes chemical combination.

(*e*) The *solubility* of the racemates is, as a rule, lower than that of the active modifications.

Examples:

100 parts of solvent dissolve at the temperature t°.

	t°.	Racemic form. Parts.	Active forms. Parts.
Tartaric or racemic acid in water	0	8·2	115·0
	20	17·0	139·4
	60	64·5	217·6
	100	137·8	343·5
Calcium glycerate in water	20	3·85	9·32
Zinc glycerate in water	20	3·87	39·03
Potassium methoxy-succinate in water	14	3·0	14·0
Calcium methoxy-succinate in water	14	0·46	5·41
Calcium gulonate in water	15	1·6	5·8
Leucine in water	—	0·98	2·44
Camphoric acid in water	20	0·24	6·96
Camphoric acid in alcohol	15	33·0	112·0

The greater insolubility of the racemic compound may often be recognised by a crystalline precipitate being formed on mixing concentrated solutions of the two active antipodes. This is shown well by *d*- and *l*-tartaric acids, and by *d*- and *l*-camphoric acids dissolved in alcohol.

In the case of certain substances, however, the racemic form is more easily soluble than the active isomers, as, for instance:

	t°.	Racemic form. Parts.	Active forms. Parts.
Mandelic acid in water	20	15·97	8·64
Silver *l*-valerate in water	20	1·18	0·08

The solubility relationship of the racemic compounds may in many cases be modified by the fact that even in concentrated solution it is not dissolved unchanged, but is split up into the active antipodes. This has been proved for racemic acid and for sodium ammonium racemate.

(*f*) The *melting point* of the racemic form is sometimes higher and sometimes lower than that of the active forms; and in one case exactly the same melting point has been found for both modifications.

	Racemic form.	Active form.	R-A.
Malic acid	130°·5	100°	+30°·5
Dimethyl racemate or tartrate	85	45	+40
Methoxysuccinic acid	108	89	+19
Mannitol	168	163·5	+ 4·5
Mannoheptitol	203	187	+16
Galactose phenylosazone	206	195	+11
Camphoric acid	202	187	+15
Limonene tetrabromide	124	105	+19
Carone semicarbazide	178	168	+10
α-Pipecoline hydrochloride	205	190	+15
Chlorosuccinic acid	153·5	176	−22·5
Bromosuccinic acid	160·5	172	−11·5
Glutaminic acid	198	202	− 4
Mandelic acid	118	132·8	−14·8
Fenchyl alcohol	34	40	− 6
β-Carvone tetrabromide	108	121	−13
Carvone semicarbazide	155	162·5	−7·5

Gulonic phenylhydrazide	147° to 149°
Phenyl-gulosazone	157 „ 159
Limonene α-nitrosochloride	103 „ 104
π-Monobromocamphor	92·4 „ 92·7

There seems to be a certain parallelism between the melting point and the density, inasmuch as in those compounds whose racemic form has a higher melting point than the active isomers, the density of the former is also higher than that of the latter.

[Walden, *Ber.* **29**, 1702 (1896), notices that the form which has the higher melting point has always the lower solubility.]

It has not yet been proved that in the case of liquid, inactive racemic compounds, produced by mixing equal quantities of the liquid active antipodes that these racemates are true chemical compounds.

14. Formation of Racemic Compounds. — Racemic compounds are produced by the following four methods:

(*a*) *Mixture of Equal Quantities of the Antipodes.* If the mixing be carried out in solution, it may happen that above a certain temperature an inversion of the system of bodies takes place in one direction, whilst below this temperature the inversion goes on in the opposite direction. There is, therefore, the possibility of the racemic body being split up into the antipodes or the formation of the former from the latter. The transition-temperature has so far only been determined in a few cases. Let us first take up the case of

sodium ammonium racemate $[Na.NH_4.C_4H_4O_6 + H_2O]_2$,

and a mixture of equal parts of

sodium ammonium *d*-tartrate, $Na.NH_4.C_4H_4O_6 + 4H_2O$,

and

sodium ammonium *l*-tartrate, $Na.NH_4.C_4H_4O_6 + 4H_2O$.

If a solution of the racemate or the mixture of the tartrates be allowed to evaporate at different temperatures, the following phenomena take place, as van't Hoff and Deventer[1] have shown:

1. If the temperature is lower than 27°C., the solution contains *d*- and *l*-tartrates, and on evaporation these two salts are deposited in enantiomorphic crystals.
2. Between the temperature limits 27° and 35° the racemate exists in solution, and can be obtained by crystallisation.
3. Above 35° the racemate is decomposed to a mixture of equal parts of sodium racemate $[Na_2.C_4H_4O_6]_2$ and ammonium racemate $[(NH_4)_2.C_4H_4O_6]_2$. The formation of these two salts may take place at 30° if crystals of the same be added to the solution.

The transition of sodium ammonium *d*- and *l*-tartrates into the racemate may also take place without being in solution. When a powdered mixture of the salts is heated to 27° racemisation takes place, and the mixture liquefies owing to part of the water of crystallisation being liberated. Inversely, a mixture of one molecule of sodium ammonium racemate with six molecules of water, which has the consistency of a syrup, becomes solid at a temperature below 27°, and then consists of the two active tartrates. This reversal process may be represented by the following equation, in which $T = C_4H_4O_6$:

---

[1] Van't Hoff and Deventer, *Zt. ph. Chem.* I, 165 (1887).

$$\left.\begin{array}{l} d\text{-}\ \mathrm{Na.NH_4.T+4H_2O} \\ l\text{-}\ \mathrm{Na.NH_4.T+4H_2O}\end{array}\right\} \begin{array}{c}\rightarrow\\ \leftarrow\end{array} \left\{\begin{array}{l}[\mathrm{Na.NH_4.T+H_2O}]_2\\ 6\mathrm{H_2O}.\end{array}\right.$$

The relationships between the following salts have also been investigated:[1]

Potassium sodium racemate $[K.Na.C_4H_4O_6 + 3H_2O]_2$,
Potassium sodium *d*- and *l*-tartrates, $K.Na.C_4H_4O_6 + 4H_2O$.

According to the temperature, in a solution prepared either from the racemate or from the two tartrates, the salts exist in the following condition:

1. Below about −6° *d*- and *l*-tartrates are present.
2. Above −6° combination to the racemate takes place. This can be considerably induced by the addition of small crystals of the racemate.
3. The racemate exists up to 41°; but on further heating it is decomposed into sodium racemate $[Na_2C_4H_4O_6]_2$, and potassium racemate $[K_2C_4H_4O_6 + 2H_2O]_2$.

Kenrick[2] has recently found that racemic ammonium bimalate decomposes into the active salts above the temperature of about 73°, according to the equation:

$$[NH_4.C_4H_5O_5 + H_2O]_2 \rightleftarrows d\text{-}NH_4.C_4H_5O_5 + l\text{-}NH_4.C_4H_5O_5 + 2H_2O.$$

---

[1] Van't Hoff and Goldschmidt, *Zt. ph. Chem.* **17**, 505 (1895).

[2] Kenrick, *Ber.* **30**, 1749 (1897). See also: van't Hoff and Dawson, *Ber.* **31**, 528 (1898).

The transition-temperature in this case is fairly high.

From these few instances it is evident that the temperature plays an important part when we desire to synthesise a racemate from the antipodes, as well as when it is required to decompose the former into the latter. The reason why success has not attended attempts to carry out either of these processes with certain substances, lies in the want of sufficient knowledge of the transition-temperatures.

(*b*) *From the Active Forms by Heating.*—Many active substances suffer a gradual diminution, and ultimate disappearance of rotatory power on long-continued heating, at the same time no change of composition taking place. This was at first attributed to a destruction of activity, but was later recognised as due to racemisation. On account of the increased motion of the atoms by the heat, a transformation into the oppositely rotating modification takes place, and finally a state of equilibrium is established, in which just as many molecules of the *d*-form are converted into *l*-form as the reverse, and so the mixture consists of equal quantities of both.

In order to bring about racemisation, it is necessary with most substances to maintain them for a long time at a temperature not lower than 160°. The following active substances can be racemised by heating them in sealed tubes with a little water for some days at a temperature of 160° to 200°: tartaric acid, aspartic acid, isopropyl-phenylglycollic acid,

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mandelic acid, camphoric acid; from tartaric acid a certain quantity of constitutionally inactive mesotartaric acid is obtained as well as racemic acid. The active terpenes and amyl alcohol suffer a gradual decrease in their rotatory power by being heated for a long time at from 250° to 300°.

In many cases the presence of certain substances accelerates the racemisation. Small quantities of concentrated sulphuric acid act in this way on the terpenes and *d*-valeric acid. Active leucine, which is not altered by heating with water to between 170° and 180°, is transformed in presence of solution of barium hydrate at between 150° and 160° into the racemic compound. Active amyl alcohol racemises more readily when some sodium is dissolved in it, or when caustic soda is added. Aluminium tartrate accelerates the conversion of tartaric acid into racemic acid.

The racemisation-temperature of some substances is quite low. Thus both *d*- and *l*-limonene monohydrochlorides lose their rotatory power after they have been kept for some time at the ordinary temperature.

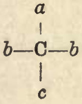
(*c*) *On the Conversion of Active Compounds into Active Derivatives.*—If an active molecule retains its constitution when it undergoes some chemical change (such as the conversion of acids into salts, esters, or amides, or alkaloids into their compounds with acids), its activity is also retained. The same is true of simple conversions, such as active amyl alcohol into valeric acid, aspargine into aspartic and malic acids, &c.

Under certain conditions the product of the reaction may become inactive by racemisation. This seems to be especially the case when an atom which is directly united to the asymmetric carbon atom takes part in the reaction. Active malic acid, $COOH—{}^*CH.OH—CH_2—COOH$, on heating in a sealed tube with hydrobromic acid yields racemic bromosuccinic acid, $COOH—{}^*CH.Br—CH_2—COOH$. Active valeric acid, $C_2H_5—{}^*CH.CH_3—COOH$, when oxidised in aqueous solution with potassium permanganate gives racemic oxyvaleric acid, $C_2H_5—{}^*C.OH.CH_3—COOH$.

In such cases if the temperature be kept low racemisation may be prevented, and the product obtained in the active form. Active chlorosuccinic acid can be prepared from active malic acid by warming with phosphorus pentachloride in chloroform solution, as the temperature cannot then rise above the boiling point (62°) of the solvent.

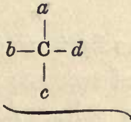
(*d*) *On the Transformation of Inactive into Active Substances.*—If a symmetric compound (I) be transformed into an asymmetric one by replacement of one of the *b* radicles by *d*, the product may have either the configuration II*a* or II*b* :

I.



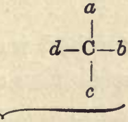
$$\begin{array}{c} a \\ | \\ b—C—b \\ | \\ c \end{array}$$

II*a*.



$$\begin{array}{c} a \\ | \\ b—C—d \\ | \\ c \end{array}$$

II*b*.



$$\begin{array}{c} a \\ | \\ d—C—b \\ | \\ c \end{array}$$

On account of the symmetry of the original molecule there is no reason why one of the active modifications should be formed in preference to the other, but rather the speed of formation of each will be the same, and so the product turn out to be racemic. Indeed, experience teaches us that all artificially prepared compounds containing one or more asymmetric carbon atoms are first obtained in the inactive, *i.e.* racemic, form. No active substance has yet been directly prepared artificially. See further § 17 [and Japp, *British Association Report*, 1898; *Nature*, **58**, 452 (1898)].

15. Resolution of Racemic Substances into the Antipodes.

—Three different ways of carrying this out are known. They were discovered by Pasteur, and first applied to racemic (tartaric) acid.

(*a*) *Resolution by Crystallisation.*—This process depends on the splitting up of dissolved racemic compounds under certain temperature conditions into the antipodes, and on evaporation these are deposited in enantiomorphic crystals which can be sorted out into dextro- and lævo- compound according to the position of the characteristic facet. In this way equal quantities of the antipodes are obtained. This is an application of the transition-temperature (which is different for each compound) mentioned in § 14 (*a*).

The method was first used by Pasteur[1] in 1848 for the resolution of racemic acid in the form of the sodium ammonium salt. An aqueous solution of racemic acid is divided into two equal parts, one of which is neutralised by caustic soda, and the other by ammonia. The two are then mixed, and the solution evaporated on the water-bath until crystals separate out on cooling. To the cooled solution sufficient water to redissolve the separated salt is added, and it is then allowed to spontaneously evaporate, care being taken that the temperature constantly remains below 27°. The crystals which are deposited are taken out from time to time, and the position of the hemihedral facets on them is determined. The formation of *d*- and *l*-crystals is greatly assisted by placing in the solution, before evaporation takes place, small crystals of both.

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[1] Pasteur, *Ann. chim. phys.* [3] **24**, 442; **28**, 56.

If the crystallographic investigation offers difficulty, the question whether a crystal is the sodium ammonium salt of *d*-tartaric or *l*-tartaric acid, or of racemic acid, can be settled by a method suggested by Anschütz,[1] which is founded on the lower solubility of calcium racemate than of either of the calcium tartrates. The crystal is washed with a little water to free it from mother-liquor, and a fragment is dissolved in a little water, and the solution divided into two parts. To one part of the solution about 3 c.c. of a saturated solution of calcium dextrotartrate is added, and the mixture allowed to stand for some time. If precipitation occurs, then a salt of lævo-tartaric acid must have been present; if no precipitation occurs, but a precipitate is formed when a solution of calcium lævo-tartrate is added to the other part of the solution, then a salt of dextrotartaric acid is denoted. If precipitation takes place in both solutions, then the crystal must have been a salt of racemic acid.

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[1] Anschütz, *Lieb. Ann.* **226**, 193 (1884).

The separation of the two sodium ammonium tartrates may also be carried out as follows: A concentrated solution of the racemate is prepared in the heat, care being taken that no solid matter remains undissolved. The solution is allowed to cool slowly, at the same time being protected from dust, until it reaches a state of supersaturation, and a small amount of crystals, either of the *d*-tartrate or of the *l*-tartrate, is dropped in. Separation of the salt the same as the crystals which were added takes place, and it is quickly sucked dry from the mother-liquor.

Fermentation lactic acid in the form of its zinc ammonium salt, $Zn.NH_4.(C_3H_5O_3)_3+3H_2O$, has been resolved by crystallisation into the *d*- and *l*-lactates, $Zn.NH_4.(C_3H_5.O_3)_3+2H_2O$. The method of supersaturation works best in this case. Racemic isohydrobenzoin, $C_6H_5-CH.OH-CH.OH-C_6H_5$ yields on evaporation of an ethereal solution enantiomorphic crystals which can easily be obtained quite a centimetre long. Hydrobenzoin is the non-decomposable inactive modification (Erlenmeyer, jun.).[1]

(*b*) *Resolution by Means of Active Compounds.*—If two antipodes combine chemically with the same active substance, two isomeric compounds are produced which have different solubilities, and which, therefore, can be separated. This offers a method for the resolution of racemic acids and bases.

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[1] Erlenmeyer, jun., *Ber.* 30, 1531 (1897).

The decomposition of racemic acids is best carried out with the aid of an alkaloid. The alkaloids usually employed are: cinchonine, cinchonidine, quinine, conchinine, strychnine, brucine, and morphine. These are all mono-acidic bases, and they are added to the racemic acid in such proportion as to form either the neutral or an acid salt. On cooling a hot saturated solution, the salt either of the *d*-acid or that of the *l*-acid separates out first. When this method is resorted to it is generally desired only to obtain one of the antipodes (the other being more easily procurable by some other method), and on this account a judicious choice of the alkaloid to be used must be made.

The process was first tried in 1853 by Pasteur[1] with racemic acid, and he found that by using cinchonine or cinchonicine the salt of *l*-tartaric acid was the more difficultly soluble one, but when quinine, quinicine, or brucine was used, the salt of *d*-tartaric acid separated out first. For the preparation of *l*-tartaric acid cinchonine is the best alkaloid to use, and the following is the procedure suggested by Marckwald.[2] One molecule of the alkaloid, $C_{19}H_{22}N_2O=294$, is used to two molecules of the acid $2C_4H_6O_6=300$, *i.e.* about equal weights. The alkaloid is added in small quantities to a boiling aqueous solution of racemic acid, then sufficient water is added to give a clear solution. On cooling, crystals of cinchonine acid *l*-tartrate are deposited, and after standing for one day, these are filtered off. The yield is about two-thirds of the theoretical. The salt is recrystallised from hot water and decomposed with ammonia; the cinchonine is filtered off and lead acetate added to the filtrate. The precipitated lead *l*-tartrate is decomposed with sulphuretted hydrogen (or better with dilute sulphuric acid when a large quantity has to be dealt with), and the free *l*-tartaric acid obtained. The mother-liquor from the cinchonine *l*-tartrate, which contains chiefly *d*-tartaric acid along with smaller quantities of *l*-tartaric acid and the salts of both, after some time deposits crystals of cinchonine *d*-tartrate, which are filtered off and treated to reobtain the base. The liquid filtered off from this *d*-tartrate is divided into two equal parts, one of which is exactly neutralised with caustic soda, the other with ammonia. Both are filtered off from cinchonine, and the united filtrates are considerably evaporated, then on cooling, sodium ammonium *d*-tartrate first separates out. The crystals are drained off and the mother-liquor further evaporated, until a sample shows inactivity or a slight lævorotatory power when examined in the polarimeter. Racemic acid is then present in the solution, which is worked up for the free acid, which is treated anew with cinchonine.

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[1] Pasteur, *Ann. chim. phys.* [3] 38, 437; *C. r.* 37, 162.

[2] Marckwald, *Ber.* 29, 42 (1896).

The following racemic acids have been resolved by means of alkaloids :

	The more difficultly soluble salt contains the :
With *d*-cinchonine :	
Malic acid	*d*- acid
Methoxysuccinic acid	*d*- "
Mandelic acid	*d*- "
Phenyl-α-bromolactic acid	*d*- "
Phenyl-αβ-dibromopropionic acid	*l*- "
Racemic acid	*l*- "
With *l*-strychnine :	
Galactonic acid	*d*- "
Phenyl-αβ-dichloropropionic acid	*d*- "
Methoxysuccinic acid	*l*- "
Lactic acid	*l*- "
With *l*-brucine :	
Phenyl-αβ-dibromopropionic acid	*d*- "
Phenyl-dibromobutyric acid	*d*- "
Valeric acid	*l*- "

As can be seen from the table, the directions of the rotations of the base and of the acid have no determining influence on the solubility of the salts formed.

The resolution of racemic bases has, up to the present, always been carried out by means of *d*- and *l*-tartaric acids, and was first performed by Ladenburg[1] with synthetically prepared conine. If the racemic base be neutralised with ordinary *d*-tartaric acid in the proportion of 1 mol. to 1 mol., the solution on evaporation yields first crystals of *d*-conine *d*-bitartrate, from which the pure *d*-base can be obtained. The *l*-base does not form a well-crystallised salt with *d*-tartaric acid, and in order to obtain the pure *l*-base, the method which Marckwald[2] worked out for *a*-pipecoline can be employed. By distillation of the mother-liquor with caustic potash, *l*-pipecoline is obtained in the free state along with a little of the *d*-base. The distillate is neutralised with *l*-tartaric acid, and well crystallised *l*-pipecoline *l*-tartrate separates out, and from it the pure *l*-base can be obtained. Racemic *a*-pipecoline has been resolved almost quantitatively into the antipodes by working up the mother-liquors several times in this way.

---

[1] Ladenburg, *Ber.* **19**, 2582 (1886).

[2] Marckwald, *Ber.* **29**, 43 (1896).

As in most cases only *d*-tartaric acid has been used, only one of the active forms has been isolated —*e.g.* *d*-ethylpiperidine, *d*-copellidine, *l*-isocopellidine, *l*-propylene diamine, *d*-tetrahydroquinaldine, &c.

(*c*) *Resolution by Means of Fungi.*—As experience has shown, certain organised ferments possess the power of bringing about the complete disappearance of one of the active components, when they grow in a solution of a racemic compound, whilst the other active form remains unaltered. The phenomenon was first observed by Pasteur[1] in 1860, when he allowed spores of *Penicillium glaucum* to develop in a solution of ammonium racemate to which a little potassium phosphate and magnesium sulphate had been added. The liquid soon became lævorotatory, and the degree of rotation steadily increased until a maximum was reached, when no more *d*-tartaric acid was present. It was later found that other racemic compounds behaved in a similar manner with different mould-fungi, such as *Penicillium*

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[1] Pasteur, *C. r.* 51, 298.

glaucum, *Mucor Mucedo*, *Aspergillus glaucus*, as also yeasts, yielding either the dextro- or the lævo-rotatory active component. By means of *Penicillium glaucum* the following active substances have been obtained from the racemic compounds:

d-lactic acid.
d-ethoxysuccinic acid.
d-mandelic acid.
d-aspartic acid.
l-tartaric acid.
l-glyceric acid.
l-glutaminic acid.
l-mannonic acid.

Some racemic alcohols can also be resolved in this way. *d*-secondary butyl-carbinol, *l*-methyl-ethyl-carbinol, *l*-methyl-propyl-carbinol, *l*-methyl-butyl-carbinol, are not attacked by the fungi, but the antipodic forms are assimilated.

One and the same fungus destroys the *d*-modification of some compounds, and the *l*- form of others; no rule has yet been recognised in this connection. It may here be mentioned that many of the observations which have been made were carried out at a time when the methods of pure culture of fungi were little understood, and probably many of the experiments were performed with impure material.

The method of carrying out a resolution by means of mould-fungus is as follows: Several 2-litre flasks are filled to about five-sixths with water, which is boiled for about a quarter of an hour in order to sterilise the flask. A cotton-wool plug, which has previously been heated to between 130° and 150° and allowed to cool, is then inserted in the neck of each flask. Then for each litre of water 3 to 5 grams of racemic compound is added, and after this has dissolved, the solution is treated with a pure-culture of the fungus. It is best to take a large quantity of the culture which is obtained from a sample of pure cultivated fungus[1] by allowing it to develop in a suitable nutritive solution. This solution can be prepared by dissolving 10 grams of gelatine and 1 litre of beer-wort or prune-juice in warm water, filtering and sterilising. Addition of special nutritive salts is not then necessary. The flasks are again closed with the cotton-wool plug and allowed to stand at the ordinary temperature for some weeks, a sample being tested from time to time in the polarimeter. When the rotatory power ceases to increase the reaction is over. The fungus-culture might be put into a smaller flask and the solution of the racemic compound allowed to flow either continuously or intermittently through it.

16. Properties of the Active Modifications.—Only in the physical properties which are of a positive and negative nature do the antipodes differ from each other. This is the case with (1) dextro- and lævo-optical rotation, (2) enantiomorphism of the crystals, and (3) pyroelectricity of the crystals. It has been observed with *d*- and *l*-tartaric acids and the tartrates, *d*- and *l*-carvoximes, fenchone oxime, *a*-carvone pentabromide, cane sugar, and milk sugar, that on cooling or on warming two opposite electrical poles are developed.[2]

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[1] To be obtained from Král's Mycological Institute, Kleiner Ring, Prague.

[2] On the pyroelectricity of the crystals see Liebisch, *Grundriss der physikalischen Krystallographie*, 1896, p. 462.

In all other physical properties the two antipodes behave exactly alike. Numerous observations have confirmed this agreement with regard to:

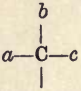
1. Density, both in the solid state and in solutions of the same concentration.
2. Melting point and boiling point.
3. Solubility.
4. Heat of solution.
5. Heat of combustion.
6. Heat of neutralisation.
7. Electrical conductivity.
8. Index of refraction.

In chemical properties the antipodes may behave similarly or differently.

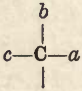
The amount of water (or other inactive material) of crystallisation contained by the two forms is exactly the same. The corresponding racemic compound may differ from them in this respect, as pointed out in § 13.

If the *d*- and *l*-forms of a substance are converted into compounds in which the originally active complex remains unchanged, and into which no new asymmetric carbon atom is introduced, then the two products differ only in the direction of their rotatory power and in the crystal form, but are otherwise identical in physical properties. This is the case when, for instance, *d*- and *l*-tartaric acids are combined with inorganic or inactive organic bases.

When the antipodes are converted by means of an active substance into new compounds which contain new asymmetric carbon atoms, then these products behave quite differently. Thus if *d*-cinchonine be saturated with (1) *d*-tartaric acid, and (2) *l*-tartaric acid, the two isomeric compounds obtained differ in their degree of rotation and also in such physical properties as solubility, &c. According to the theory of van't Hoff the difference is due to the fact that when a right and a left asymmetric group:

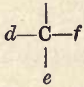


$$\begin{array}{ccc} & b & \\ & | & \\ a - & \mathrm{C} & - c \\ & | & \end{array}$$



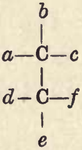
$$\begin{array}{ccc} & b & \\ & | & \\ c - & \mathrm{C} & - a \\ & | & \end{array}$$

become united to the same asymmetric complex:

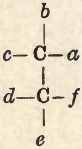


$$\begin{array}{ccc} & | & \\ d - & \mathrm{C} & - f \\ & | & \\ & e & \end{array}$$

the two products formed:



$$\begin{array}{ccc} & b & \\ & | & \\ a - & \mathrm{C} & - c \\ & | & \\ d - & \mathrm{C} & - f \\ & | & \\ & e & \end{array}$$



$$\begin{array}{ccc} & b & \\ & | & \\ c - & \mathrm{C} & - a \\ & | & \\ d - & \mathrm{C} & - f \\ & | & \\ & e & \end{array}$$

are not mirror-images of each other.

The method of separating the antipodes given in § 15 (*b*) is founded on this difference.

Some physiological differences which have been observed between antipodes may be connected with these relationships. E. Fischer[1] has found that when yeast acts on the *d*- and *l*-forms of different sugars only one is subjected to fermentation, the other remaining unchanged.

---

[1] E. Fischer, *Ber.* **23**, 382, 389, 2621 (1890); **25**, 1259 (1892); **27**, 2031, 2035, 2985, 3479 (1894); **28**, 1429 (1895).

The following:

ferment:	do not ferment:
d- (+) glucose	*l*- (−) glucose
d- (+) mannose	*l*- (−) mannose
d- (+) galactose	*l*- (−) galactose
d- (−) fructose	*l*- (+) fructose

Mould-fungi produce analogous phenomena in their action on many racemic compounds, as already mentioned in § 15 (*c*), as also do certain non-organised ferments (enzymes) in the decomposition of glucosides.

The explanation of this selective action may be, that the enzymes as well as the organised ferments contain albuminoids which are active and always lævorotatory. On this account a dissimilar behaviour towards the two antipodes may be occasioned.

Isomeric sugars which have the same direction of rotation are differently attacked by yeast, and this shows that not only the direction of rotation, but also the configuration of the molecule, influences this action. E. Fischer has found that

d-glucose and *d*-mannose . .	ferment easily,
d-galactose	ferments more difficultly
d-talose	does not ferment.

As has already been remarked, the resolution of racemic acids by alkaloids (§ 15, *b*), and the action of mould-fungi on racemic compounds shows no regular influence of the direction of rotation.

Lastly, it may be mentioned that other physiological differences between antipodes have been observed with reference to taste and poisonousness. Piutti found that *d*-asparagine tastes sweet, whilst *l*-asparagine is insipid. According to Chabrié, *l*-tartaric acid in large doses is about double as poisonous as *d*-tartaric acid.

17. Formation of the Active Isomers.—This may occur in the following ways:

(*a*) *From Inactive Material. Artificial Preparation of Active Compounds.*—The fact that when naturally occurring active compounds are prepared synthetically they are always inactive, formerly led to the view that substances possessed of rotatory power could only be produced in plant or animal cells.[1] This view was taken up by Pasteur, but had to be abandoned as proof was collected that the inactivity of the artificial products was due to their racemic nature. In 1873 Jungfleisch carried out the first complete synthesis of an active compound—namely, *d*-tartaric acid. Starting with ethylene, he prepared ethylene bromide, ethylene cyanide, succinic acid, dibromosuccinic acid, then racemic acid, which was resolved. The first active alkaloid to be artificially prepared was *d*-conine, which Ladenburg obtained by splitting up synthetic *a*-propyl-piperidine by means of tartaric acid.

From the doctrine of the asymmetric carbon atom van't Hoff has drawn the following conclusions with reference to the synthesis of active compounds:

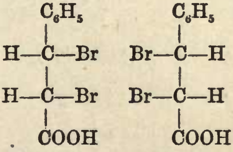
---

[1] [See Japp, *Report of Brit. Assoc.*, 1898. Presidential address to the chemical section.]

1. When a substance prepared from a symmetric compound contains only one asymmetric carbon atom, then a single racemic body is formed. The same is true when the compound produced contains two asymmetric carbon atoms, but whose molecule consists of two similar parts. From succinic acid only one racemic dibromosuccinic acid can be produced.

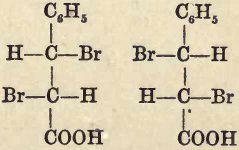
2. If from the inactive substance a molecule is formed which contains two asymmetric carbon atoms, and does not consist of two similar parts, then the simultaneous formation of two racemic pairs is possible, and by the resolution of these, four active isomers can be obtained. It is not necessary that both racemic isomers be formed in equal quantity, for on account of different stability the formation of one of them in the reaction may take place in preference to the production of the other.

Thus, from cinnamic acid, $C_6H_5.CH{=}CH.COOH$, the following cinnamic acid dibromides may be formed:



$$\underbrace{\begin{array}{c} C_6H_5 \\ | \\ H{-}C{-}Br \\ | \\ H{-}C{-}Br \\ | \\ COOH \end{array} \qquad \begin{array}{c} C_6H_5 \\ | \\ Br{-}C{-}H \\ | \\ Br{-}C{-}H \\ | \\ COOH \end{array}}$$

First racemic compound.



$$\underbrace{\begin{array}{c} C_6H_5 \\ | \\ H{-}C{-}Br \\ | \\ Br{-}C{-}H \\ | \\ COOH \end{array} \qquad \begin{array}{c} C_6H_5 \\ | \\ Br{-}C{-}H \\ | \\ H{-}C{-}Br \\ | \\ COOH \end{array}}$$

Second racemic compound.

The inactive bromination-product of cinnamic acid, according to Liebermann and Hartmann,[1] does not contain both racemic compounds, but only one. The resolution of this has led to antipodes with $[\alpha]_D = +55°$ and $-41°$. The other racemic compound has been obtained by Liebermann[1] by bromination of the unstable allocinnamic acid, and has been almost completely separated into the components with $[\alpha]_D = +64°$ and $-71°$.

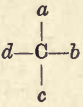
---

[1] Liebermann and Hartmann, *Ber.* **26**, 1664 (1893).

(*b*) *From Active Material.*—The following cases may occur:

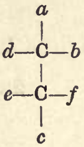
1. A compound with one asymmetric carbon atom may be transformed into one with two such atoms. According to the theory of van't Hoff and Le Bel an active molecule C*abcd*, the dextrorotatory configuration of which will be represented by I., will yield on the introduction of the group $e-\overset{|}{\underset{|}{C}}-f$ the two isomeric products I. *a* and I. *b* which are not the antipodes of each other. These latter do not possess the same properties, and may therefore be formed in unequal quantities. In the same way from the lævorotatory configuration II. two non-antipodic isomers result:

I.



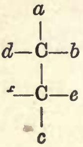
$$\begin{array}{c} a \\ | \\ d-C-b \\ | \\ c \end{array}$$

I.*a*



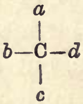
$$\begin{array}{c} a \\ | \\ d-C-b \\ | \\ e-C-f \\ | \\ c \end{array}$$

I.*b*



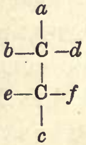
$$\begin{array}{c} a \\ | \\ d-C-b \\ | \\ f-C-e \\ | \\ c \end{array}$$

II.



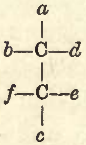
$$\begin{array}{c} a \\ | \\ b-C-d \\ | \\ c \end{array}$$

II.*a*



$$\begin{array}{c} a \\ | \\ b-C-d \\ | \\ e-C-f \\ | \\ c \end{array}$$

II.*b*



$$\begin{array}{c} a \\ | \\ b-C-d \\ | \\ f-C-e \\ | \\ c \end{array}$$

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[1] Liebermann, *Ber.* 27, 2037 (1894).

Thus the dextro- or lævorotatory substance yields no racemic compound, but a mixture of two active isomers which possess different rotatory powers. The relationship is, therefore, different from that in the case of the synthesis from inactive materials.

Of the four above isomers I. *a* and II. *b* are antipodes, as also are I. *b* and II. *a*; and these may combine to two racemic compounds. A mixture of these two racemates must result when the racemate I. + II. of the original substance is subjected to the chemical transformation, and the product of the reaction will be inactive.

It is, of course, evident that the result will be the same if the new asymmetric carbon atom is not introduced by a synthetic process, but is produced from one of the symmetric carbon atoms of the compound.

The above results may be expressed, as van't Hoff[1] first showed, in the following manner, if we denote the two asymmetric groups contained in the four isomers by ±A and ±B:

$$\text{The original } + \text{ compound yields } \begin{cases} +A+B \\ +A-B \end{cases}$$

$$\text{The original } - \text{ compound yields } \begin{cases} -A+B \\ -A-B \end{cases}$$

and the two antipode-pairs are:

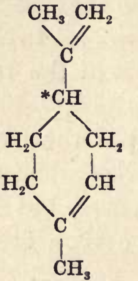
$$\left.\begin{matrix} +A+B \\ -A-B \end{matrix}\right\} \text{ and } \left.\begin{matrix} +A-B \\ -A+B \end{matrix}\right\}.$$

---

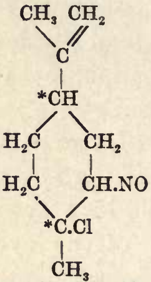
[1] Van't Hoff, *La chimie dans l'espace*, 1875, p. 17–28. *Die Lagerung der Atome im Raume*, 1894, p. 45.

If we know the specific rotations of the four isomers, we can calculate the value for the rotation of the groups A and B.

These theoretical previsions have been experimentally confirmed in many instances. Limonene on treatment with amyl nitrite and hydrochloric acid in presence of acetic acid is transformed into the nitrosochloride compound $C_{10}H_{16}.NOCl$. These substances have probably the constitutions:



Limonene.



Limonene nitrosochloride.

According to Wallach,[1] two isomers (*α* and *β*) of the nitrosochloride are always produced, and can be separated by their different solubilities in ether.

From + limonene	*α*-nitrosochloride	$[\alpha]_D = +313{\cdot}4$
	β-nitrosochloride	$[\alpha]_D = +240{\cdot}3$
From − limonene	*α*-nitrosochloride	$[\alpha]_D = -314{\cdot}8$
	β-nitrosochloride	$[\alpha]_D = -242{\cdot}2$

The two *α*- and the two *β*- compounds appear, therefore, to be optical antipodes.

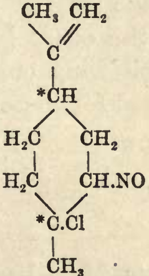
In the reaction the *α*-nitrosochlorides are always formed in greater quantity than the *β*-; the *α*- compounds crystallise in well-formed monoclinic prisms, are easily soluble in ether, and decompose on keeping; the *β*- derivatives separate only in small crystals, are difficultly soluble in ether, but are much more stable. The *a*- and *β*- isomers behave chemically alike, but the latter in benzene solution shows a double molecular weight (Wallach[1]).

---

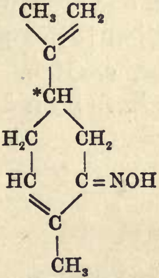
[1] Wallach, *Lieb. Ann.* **252**, 108, 145 (1889); **270**, 171 (1892).

Dipentene (*d*-*l*-limonene) yields an inactive product which is a mixture of two racemic compounds (Wallach[2]).

The asymmetry of one of the two asymmetric carbon atoms in limonene nitrosochloride may be destroyed. This can be effected by treating the nitrosochlorides with alcoholic caustic potash, whereby H + Cl is eliminated and carvoximes $C_{10}H_{14}.NOH$ are produced.



Limonene nitrosochloride.



Carvoxime.

Carvoxime occurs only in two forms (*d*- and *l*-); both *a*- and *β*-nitrosochlorides from the same limonene must, therefore, yield the same product. Wallach[3] has found that this is actually the case; and,

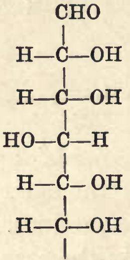
[1] Wallach, *Ber.* **28**, 1308 (1895). [2] *Lieb. Ann.* **270**, 175 (1892).
[3] *Lieb. Ann.* **246**, 227 (1888.)

further, that by the conversion change of sign (direction) of the rotation takes place :

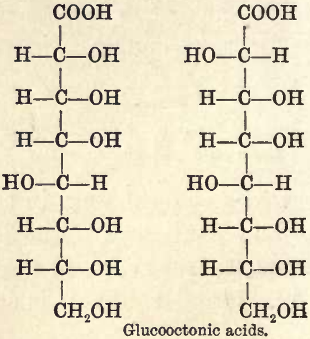
$$\text{From} + \left\{\begin{array}{l}\alpha\text{-nitrosochloride}\\ \beta\text{-nitrosochloride}\end{array}\right\} -\text{carvoxime } [\alpha]_D = -39{\cdot}3^\circ$$

$$\text{From} - \left\{\begin{array}{l}\alpha\text{-nitrosochloride}\\ \beta\text{-nitrosochloride}\end{array}\right\} +\text{carvoxime } [\alpha]_D = +39{\cdot}7$$

2. When in a substance containing several asymmetric carbon atoms the number of these is increased by one, the results obtained are the same as those given above—the new compound must exist in two isomeric forms. E. Fischer[1] has experimentally proved this by showing that from *l*- *α*-glucoheptose, $C_7H_{14}O_7$ ($[\alpha]_D = -19{\cdot}7^\circ$ in water, $c=100$), by means of the hydrocyanic acid reaction two different glucooctonic acids, $C_8H_{16}O_9$, can be obtained, one of which, in the form of lactone, has the rotation $[\alpha]_D = +45{\cdot}9^\circ$, the other $[\alpha]_D = +23{\cdot}6^\circ$ (in water, $c=100$). The following configurational formulæ have been determined for these :



α-Glucoheptose.



Glucooctonic acids.

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[1] E. Fischer, *Lieb. Ann.* **270**, 64 (1892).

In the same way from rhamnose, $C_6H_{12}O_5$, two isomeric rhamnohexonic acids, $C_7H_{14}O_7$, are obtained; the lactones of these have the rotations $[a]_D = +83{\cdot}8°$ and $43{\cdot}3°$ (Fischer and Piloty[1]). From mannose, however, by the hydrocyanic acid reaction, only one of the two mannoheptonic acids, $C_7H_{14}O_8$, has been obtained; *d*-mannose gives a lævorotatory lactone ($[a]_D = -74{\cdot}2°$), *l*-mannose a dextrorotatory one ($[a]_D = +75{\cdot}2°$). Thus from *d*- and *l*-mannose the two corresponding antipodes were obtained which could be united to a crystallisable racemic compound. This shows that the formation of one of the two possible isomers can take place in preference to the other. (Fischer,[2] Smith,[3] Hartmann.[4])

3. An increase in the number of asymmetric carbon atoms takes place when active bases combine with active acids; consequently the product must be able to exist in two different antipode-pairs. The following salts of this nature have been prepared:

Marckwald[5] combined *d*- and *l*-*a*-pipecolines with *d*- and *l*-tartaric acids to form acid tartrates, and determined the amount of water of crystallisation contained by the four salts, as also their crystal form and melting point. He carried out the same with the racemic base and racemic acid, and obtained the following results:

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[1] Fischer and Piloty, *Ber.* **23**, 3104 (1890).

[2] Fischer and Hirschberger, *Ber.* **22**, 370 (1889); Fischer and Passmore, Ber. **23**, 2226 (1890).

[3] Smith, *Lieb. Ann.* **272**, 182 (1893).

[4] Hartmann, *Lieb. Ann.* **272**, 190.

[5] Marckwald, *Ber.* **29**, 43 (1896.)

	Water of crystallisation	Crystal form	Melting point	
			Crystallised	Anhydrous
+ tartaric acid, + α-pipecoline – ,, ,, – ,, ,,	2 mol.	monoclinic hemimorphic enantiomorphic	65–66°	111–112°
+ ,, ,, – ,, ,, – ,, ,, + ,, ,,	1 mol.	?	45–46	126
r ,, ,, r ,, ,,	1 mol.	monoclinic	85	—

The acid tartrates of *d*- and *l*-limonene *a*-nitrolbenzylamine, $C_{10}H_{16}.NO.NH.CH_2C_6H_5$, have been polarimetrically examined by Wallach and Conrady.[1] The following are the results obtained, using aqueous alcoholic solutions containing from 0·97 to 1·38 per cent. of salt:

$$\left\{\begin{array}{l} + \text{ tartaric acid, } + \text{ base} \ldots\ldots [\alpha]_D = -49{\cdot}9^\circ \\ - \quad ,, \quad ,, \quad - \quad ,, \ldots\ldots \quad ,, = +51{\cdot}0 \end{array}\right.$$

$$\left\{\begin{array}{l} + \quad ,, \quad ,, \quad - \quad ,, \ldots\ldots \quad ,, = +69{\cdot}6 \\ - \quad ,, \quad ,, \quad + \quad ,, \ldots\ldots \quad ,, = -69{\cdot}9 \end{array}\right.$$

From these data the values calculated for the rotatory powers are:

$$\begin{array}{ll} + \text{ base} = -60^\circ & + \text{ acid} = +10^\circ \\ - \quad ,, \quad = +60 & - \quad ,, \quad = -10. \end{array}$$

Therefore, when these bases are combined to tartaric acid, a reversal of their direction of rotation takes place.

The following results have been obtained by Fileti[2] for salts of *d*- and *l*-isopropyl-phenyl-glycollic acid and quinine and also cinchonine:

	Melting point	$[\alpha]_D$
+ Isopropyl-phenyl-glycollic acid, – quinine	192–193°	– 79·4°
– ,, ,, ,, – ,,	204–205	–118·4
+ ,, ,, ,, + cinchonine	201	+136·8
– ,, ,, ,, + ,,	167	+ 83·4

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[1] Wallach and Conrady, *Lieb. Ann.* **252**, 148 (1889).

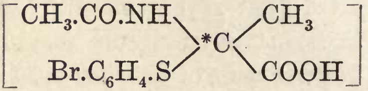
[2] Fileti, *Ber.* **26**, iv., 89 (1893).

Here again we see the formation of two non-antipodic isomers.

(*c*) *Formation of Active Compounds in Plant and Animal Cells.*—It might be expected that in the formation of asymmetric compounds from inactive material in plant cells both antipodes would be formed, as in the artificial synthesis, and that racemic compounds would result. It might further be anticipated that several or all of the different configurations of the molecule would be formed. So far as experience yet teaches us, however, only one of such isomers is produced, and that almost without exception only in one of the active forms. Of the hexoses only dextrorotatory *d*-glucose, of the ketoses only lævorotatory *d*-fructose, and of the four possible tartaric acids only the dextro-active modification appear to be formed in nature. The same applies to the whole group of plant substances, such as the bitter principles and alkaloids which are only found in one of the active forms. In turpentine oil obtained from different species of Abietineæ [firs and pines], as also in other ethereal oils, there occur either *d*-pinene and *d*-limonene or *l*-pinene and *l*-limonene; and at the same time dipentene has been found in some of these, and so here we have a case of the formation of a racemic compound in a plant.

No explanation of these phenomena has yet been given.

In the animal organism which consists chiefly of asymmetric substances, and which is nourished particularly by such, the formation of active compounds may take place either by synthetical or analytical processes. There is, however, the possibility of inactive substances which are present taking part in the transformations, and so being converted into active compounds. This is proved, for instance, by the observation that bromobenzene taken into the system appears in the urine as active bromophenylmercapturic acid



$$\left[\begin{matrix}\mathrm{CH_3.CO.NH} \\ \mathrm{Br.C_6H_4.S}\end{matrix} > {}^{*}\mathrm{C} < \begin{matrix}\mathrm{CH_3} \\ \mathrm{COOH}\end{matrix}\right].$$

It is worthy of note that the albumens of both animal and vegetable origin are, without exception, lævorotatory, as are also the gelatines. The acids of the bile are almost all dextrorotatory.

18. Transformation of one Antipode into the other.—A general method by which one half of an active substance can be converted into the oppositely rotating isomer consists in racemising the substance by heating (v. § 14, *b*), then resolving the product (v. § 15). In this manner Lewkowitsch has succeeded in obtaining *d*-mandelic acid from the *l*-acid. This process is, however, of limited applicability, for many substances can be racemised only with difficulty, and in the case of others racemisation cannot be carried out at all.

A direct reversal of the direction of rotation was first observed by Beckmann[1] with *l*-menthone ($[\alpha]_D = -24\cdot8^\circ$ to $28\cdot5^\circ$). On treatment with 90 per cent. sulphuric acid, this is converted into a dextrorotatory variety ($[\alpha]_{\mathrm{D}} = +26{\cdot}3°$ to $28{\cdot}1°$). The two isomers, however, do not seem to be true antipodes, for on treating them with hydroxylamine two menthone-oximes of quite different properties are formed. From *l*-menthone a crystallisable oxime with rotation $[\alpha]_{\mathrm{D}} = -40{\cdot}8°$ to $42°$ in alcoholic solution is obtained, whilst *d*-menthone yields a thick syrupy oxime which is also lævorotatory, $[\alpha]_{\mathrm{D}} = -4{\cdot}9°$ to $6{\cdot}7°$. If either of these menthones be warmed with dilute acid or alkali, it is partially transformed into the other; but no racemic inactive mixture is obtained, both yielding the same dextrorotatory product. These phenomena may be explained by the fact that menthone, as the formula

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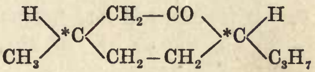
[1] Beckmann, *Lieb. Ann.* 250, 322 (1889); 289, 362 (1896).



shows, contains two asymmetric groups. If in the chemical action one of these remains intact, then on inversion of the other two isomers which are not mirror-images of each other should be formed (v. § 16).

Walden[1] has succeeded in carrying out a reciprocal conversion of true antipodes. Malic acid treated in chloroform solution with phosphorus pentachloride or pentabromide, gives chloro- or bromosuccinic acid. The halogen in this may be replaced by hydroxyl, by (1) silver oxide, (2) by caustic potash; and a conversion of the original isomer may take place. Walden has found that:

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[1] Walden, [*Ber.* **28**, 2766 (1895)]; **29**, 133 (1896); Walden and Lutz, **30**, 2795 (1897); Walden, **30**, 3147.

1. On treating malic acid with PCl_5:

d-malic acid is transformed into *l*-chlorosuccinic acid
l- „ „ „ „ *d*- „ „
} direction of rotation reversed.

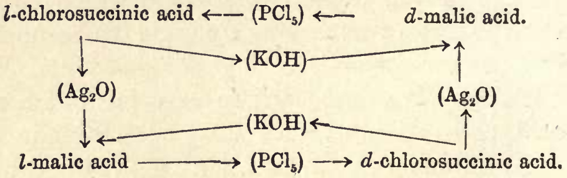
2. On heating the chlorosuccinic acids which have been neutralised by alkali with silver oxide:

d-chlorosuccinic acid is transformed into *d*-malic acid
l- „ „ „ „ *l*- „
} direction of rotation unchanged.

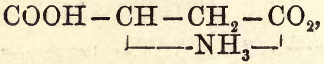
3. If the chlorosuccinic acids be warmed with aqueous or alcoholic caustic potash (or aqueous barium hydrate):

d -chlorosuccinic acid is transformed into *l*-malic acid
l - „ „ „ „ *d*- „
} direction of rotation reversed.

By means of these reactions the following cyclic processes may be carried out:



The conversion of the chlorosuccinic acids into malic acids can be carried out instead of with caustic potash, with a solution of ammonia in methyl alcohol; aminosuccinic acid,



$$COOH-\underset{\llcorner\!-\!-NH_3-\!\lrcorner}{CH-CH_2-CO_2},$$

is first formed, and this, on boiling with a solution of barium hydrate, is converted into barium malate. In this way:

d-chlorosuccinic acid is transformed into *l*-aminosuccinic acid . . . . *l*-chlorosuccinic acid is transformed into *d*-aminosuccinic acid	direction of rotation reversed.
d-aminosuccinic acid is transformed into *d*-malic acid *l*-aminosuccinic acid is transformed into *l*-malic acid	direction of rotation unchanged.

It was proved by determining the specific rotation that the inverted malic acid was the true antipode of the original acid.

Another case of this kind is the conversion of *d*-lactic acid into *l*-lactic acid through the intermediary production of chloropropionic acid, which was carried out by Purdie and Williamson.[1]

Armstrong[2] has attempted to explain how the change of the direction of rotation may take place by the transformation of malic acid into chlorosuccinic acid.

19. Transformation of Active Isomers of Different Configuration into each other.—These transformations were discovered by E. Fischer[3] in the acids of the sugar group. They take place when these acids are heated with quinoline or pyridine to 130°-150°; the object of using such bases is to prevent the formation of lactones which retard the reaction. According to the observations so far made a rearrangement of the H and OH takes place on the asymmetric carbon atom contiguous to the carboxyl group; the reaction always appears to be reversible, so that the product consists of a mixture of the original and the new acids. The following stereoisomeric acids have been transformed into each other by this method:

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[1] Purdie and Williamson, *J. C. S.* **69**, 837 (1896).

[2] Armstrong, *Proc. C. S.* No. 161, 1896, p. 45.

[3] E. Fischer, *Ber.* **23**, 799 (1890); **24**, 2137, 3622 (1891); **27**, 3193 (1894).

$C_5H_{10}O_6$	*l*-arabonic acid	$\rightleftarrows$	*l*-ribonic acid
	$A^{\times\,\times\,\bullet}_{\bullet\,\bullet\,\times}Y$		$A^{\times\,\times\,\times}_{\bullet\,\bullet\,\bullet}Y$
$C_6H_{12}O_7$	*d*-gluconic acid	$\rightleftarrows$	*d*-mannonic acid
	$A^{\bullet\,\bullet\,\times\,\bullet}_{\times\,\times\,\bullet\,\times}Y$		$A^{\bullet\,\bullet\,\times\,\times}_{\times\,\times\,\bullet\,\bullet}Y$
	l-gluconic acid	$\rightleftarrows$	*l*-mannonic acid
	$A^{\times\,\times\,\bullet\,\times}_{\bullet\,\bullet\,\times\,\bullet}Y$		$A^{\times\,\times\,\bullet\,\bullet}_{\bullet\,\bullet\,\times\,\times}Y$
	d-galactonic acid	$\rightleftarrows$	*d*-talonic acid
	$A^{\bullet\,\times\,\times\,\bullet}_{\times\,\bullet\,\bullet\,\times}Y$		$A^{\bullet\,\times\,\times\,\times}_{\times\,\bullet\,\bullet\,\bullet}Y$
	l-gulonic acid	$\rightleftarrows$	*l*-idonic acid
	$A^{\bullet\,\times\,\bullet\,\bullet}_{\times\,\bullet\,\times\,\times}Y$		$A^{\bullet\,\times\,\bullet\,\times}_{\times\,\bullet\,\times\,\bullet}Y$

$A = CH_2OH$, $Y = COOH$, $\bullet = H$, $\times = OH$.

Besides these, other cases are known.

20. Configurationally Inactive Non-decomposable Modifications.—This type may occur, as has been mentioned in the section dealing with the possible number of stereoisomers of compounds containing asymmetric carbon atoms (§ 12), with those molecules whose formula consists of two similar halves. The inactivity is due to each half having the same degree of rotatory power but of opposite directions, and these exactly compensate each other in their actions.

The correctness of this explanation follows from the fact that when the symmetry of such a molecule is disturbed an active product is obtained. This was first proved by E. Fischer.[1] He found that inactive mucic acid, $CO_2H-(CHOH)_4-CO_2H$, on reduction gives racemic galactonic acid $CHO-(CHOH)_4-CO_2H$, which can be split up into the active components ; and he also found that, inversely, active galactonic acids, as well as the galactoses, on oxidation yield inactive non-decomposable mucic acid.

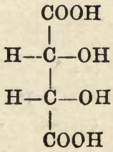
Configurationally inactive isomers occur in the following classes of symmetric compounds:

(*a*) Chain compounds containing an even number of asymmetric carbon atoms.

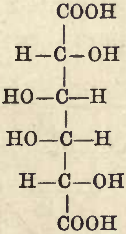
Type : $R-(^{*}Cab)_{2,4,6,\ldots}-R$. (v. § 12. Class II.)

If n is the number of asymmetric carbon atoms, the possible number of configurationally inactive isomers can be found from the formula : $i=2^{\frac{n}{2}-1}$.

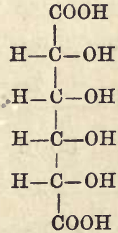
The following are examples of this class of inactive isomers :



Mesotartaric acid



Mucic acid



Allomucic acid

Other formulæ are represented on p. 66.

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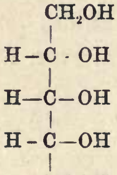
[1] E. Fischer, *Ber.* **25**, 1247, 1260 (1892).

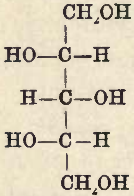
(*b*) Chain compounds containing an odd number of asymmetric carbon atoms of the

Type: $R-({}^{*}Cab)_{3,5,7....}-R$. (v § 12. Class III.) in those cases where the centre carbon atom is united to two similar chains of opposite asymmetry, and which consequently annul each other in their optical action. The possible number of inactive isomers is given by the formula: $i=2^{\frac{n-1}{2}}$.

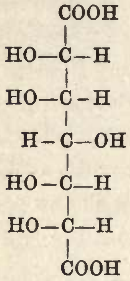
Examples:



Adonitol

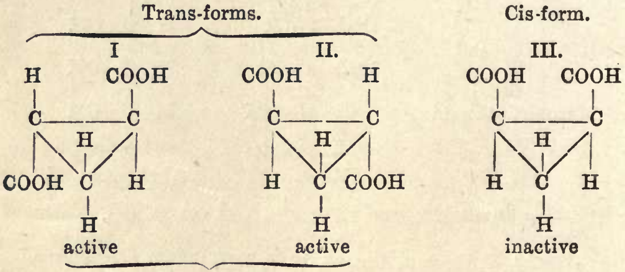


Xylitol



α-pentoxypimelic acid (from α-glucoheptose).

(*c*) The cis-forms of cyclic compounds. The simplest case is represented by trimethylene 1-2-dicarboxylic acid, where three isomers are possible:



racemic form.

The asymmetric formulæ I. and II., which are mirror-images of each other, correspond to the active forms, whilst formula III. possesses a plane of symmetry through the CH_2 group, and accordingly represents the inactive type. The same principles may be applied to hexahydrophthalic acids, hexahydroisophthalic acids, Δ^2-tetrahydroterephthalic acids, &c., in which cases the racemic modification (trans-form) and the constitutionally inactive isomer (cis-form) are known.

21. Differences in the Properties of Racemic and Configurationally Inactive Isomers.

(*a*) *Amount of Water of Crystallisation.*—This sometimes differs in the two isomers. Example:

Calcium mesotartrate	$Ca.C_4H_4O_6 + 3H_2O$.
„ racemate	$Ca.C_4H_4O_6 + 4H_2O$.
„ *d*- and *l*-tartrate	$Ca.C_4H_4O_6 + 4H_2O$.
	(Anschütz.[1])

Free mesotartaric acid crystallises with one molecule of water, as does also racemic acid; the active tartaric acids on the other hand are anhydrous.

(*b*) *Melting Point.*—As can be seen from the following table, the melting point of the racemic compound is generally higher than that of inactive modification; the opposite may, however, be the case. It is, nevertheless, possible that in the observations with erythritol and its derivatives, where the melting point of the inactive compound was found to be the higher, a true racemic compound was not used, but a mixture.

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[1] Anschütz, *Lieb. Ann.* **226**, 197 (1884).

—	Racemic inactive	Config. inactive	Diff. R−C	Observer
Racemic acid, mesotartaric acid (anhydrous)	205–206°	140–143°	+64°	Bischoff and Walden.[1]
Dimethylsuccinic acid . . .	194	120	+74	Walden.[2]
Diethylsuccinic acid	192	128	+64	,,
Diphenylsuccinic acid . . .	229	183 (220)	+46 (9)	,,
Dimethylglutaric acid . . .	122–127	99–101	+24·5	,, [3]
Erythritol	72	118	−46	Griner.[4]
Erythritol dibromohydrin . .	83	135	−52	,,
Erythritol dibromacetin . . .	96	133–134	−37·5	,,
Trimethylene 1-2-dicarboxylic acid .	175	139	+36	Buchner.[5]
Hexahydrophthalic acid . . .	215	192	+23	v. Baeyer.[6]
Hexahydroisophthalic acid . .	118–120	161–163	−43	Perkin.[7]
Δ^2-tetrahydroterephthalic acid. .	220	150–155	+67	v. Baeyer.[8]

(*c*) *Solubility.*—In every case so far investigated the configurationally inactive form has been found to be more soluble than the racemate.

100 parts of water dissolve:

—	Racemic inactive	Config. inactive	Active	Observer
	Pts.	Pts.	Pts.	
Tartaric acid, anhydrous, at 15° .	17·1	125·0	132·2	Bischoff and Walden[9]
Acid potassium tartrate, at 19° .	0·555	12·5	0·535	
Δ^2-tetrahydroterephthalic acid in cold water	0·170	2·70	—	v. Baeyer.[10]

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[1] Bischoff and Walden, *Ber.* **22**, 1815 (1889).

[2] Walden, *Zt. ph. Chem.* **8**, 467 (1891). [3] *Ibid.* 487.

[4] Griner, *C. r.* **116**, 723 (1893); **117**, 553 (1893).

[5] Buchner, *Ber.* **23**, 703 (1890).

[6] V. Baeyer, *Lieb. Ann.* **258**, 218 (1890).

[7] Perkin, *J. C. S.* **59**, 813 (1891).

[8] V. Baeyer, *Lieb. Ann.* **251**, 308 (1889).

[9] Bischoff and Walden, *Ber.* **22**, 1817 (1889).

[10] V. Baeyer, *Lieb. Ann.* **251**, 307–308 (1889).

(*d*) *Dissociation-constant*, K; determined from the electric conductivity. No regularity has yet been found.

—	Racemic inactive K	Config. inactive K_1	Diff. $K-K_1$	Observer
Racemic, mesotartaric acid . .	0·097	0·060	+0·037	Bischoff and Walden.[1]
Dimethylsuccinic acid . . .	0·0191	0·0123	+0·0068	Walden.[2]
Diethylsuccinic acid	0·0245	0·0343	−0·0098	"
Diphenylsuccinic acid . . .	0·020	0·026	−0·006	"
Dimethylglutaric acid . . .	0·0055	0·0055	0	"[3]

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[1] Bischoff and Walden, *Ber.* **22**, 1815 (1889).

[2] Walden, *Zt. ph. Chem.* 8, 467 (1891).

[3] *Ibid.* 487.

III. Connection between Degree of Rotation and Chemical Constitution.

22. Preliminary Remarks.—A very large number of investigations have been made with the object of throwing light on this problem; only few of these have, however, produced satisfactory results. By comparing the rotatory powers of the members of certain groups many have been led to the belief that definite regularities could be recognised, but such conclusions have almost always had to be laid aside on account of exceptions. The reason of this may be the uncertainty with which the specific rotation of many substances can be determined. In the case of solids which can only be examined in solution, the rotation varies with the concentration and the nature of the solvent, and it is only in few instances that comparable values can be arrived at. Consequently, we are thrown back on observations made on liquid substances, but these also cannot be implicitly trusted. If in the preparation of the substance a violent reaction takes place, or if the temperature for any reason rises too high, then a partial racemisation may occur (v. § 14, *b*), and the product will have too low a rotation. A similar change takes place when certain substances are kept for a long time, as has been shown with limonene monohydrochloride. Lastly, certain substances polymerise; according to § 6, p. 27, however, this circumstance seems to be without effect on the rotation.

In the course of these investigations active amyl esters have been largely used, and these have all been prepared from commercial laevorotatory amyl alcohol of varying activity (*e.g.* $[\alpha]_D = -4{\cdot}5°$, Guye; $-4{\cdot}78°$, Walden). All such preparations contain a certain undeterminable quantity of an inactive isomer, and can only rationally be compared with each other when they are obtained from the same specimen of active amyl alcohol. The different isomers of the crude amyl alcohol seem all to be attacked in the chemical reaction to about the same extent, for Guye and Chavanne[1] found that the alcohol regenerated from some esters by saponification had almost exactly the same rotation as that from which the ester was originally prepared.

In the following comparisons the molecular rotations, $[M] = \frac{M}{100}[\alpha]$, are used when compounds of different composition are being considered; for the comparison of isomeric substances the specific rotations, $[\alpha]$, of course, suffice.

23. Isomeric Compounds.—An idea of the relationships may be gathered from the following observations:

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[1] Guye and Chavanne, *Bull.* [3] 15, 275 (1896).

(*a*) *Metamerism, Structural-Isomerism.*

1. Different position of the active radicle:

Amylacetic acid	$[\alpha]_D = +8{\cdot}53$	Walden, *Zt. ph. Chem.* **15**, 638 (1894).
Amyl acetate	,, $= +2{\cdot}50$	
Diamylacetic acid	,, $= +18{\cdot}27$	,,
Amyl amylacetate	,, $= +7{\cdot}01$	
Methyl valerate	,, $= +16{\cdot}83$	Guye and Chavanne, *Arch. phys. nat.* [4] **1**, 54.
Amyl formate	,, $= +2{\cdot}01$	

In those cases large differences occur.

2. Alcoholic radicle active, isomerism in the inactive acidic radicle:

Amyl *n*-butyrate	$[\alpha]_D = +2{\cdot}97$	Walden, *Zt. ph. Chem.* **15**, 638 (1894).
,, iso- ,,	,, $= +2{\cdot}83$	
,, *n*-bromobutyrate	,, $= +2{\cdot}27$	,,
,, iso- ,,	,, $= +2{\cdot}53$	

The differences in the specific rotation are small.

3. Alcoholic radicle inactive, isomerism in the active acidic radicle:

Methyl *n*-butyrylmalate	$[\alpha]_D = -22{\cdot}44$	Walden, *Zt. ph. Chem.* **17**, 245 (1895).
,, iso- ,,	,, $= -22{\cdot}36$	
Ethyl *n*- ,,	,, $= -22{\cdot}22$	,,
,, iso- ,,	,, $= -21{\cdot}99$	
,, α-bromo-*n*-butyrylmalate	,, $= -24{\cdot}76$	,,
,, ,, ,, iso- ,,	,, $= -22{\cdot}57$	

The differences are again small.

4. Acidic radicle active, isomerism in the inactive alcoholic radicle:

N-butyl valerate	$[\alpha]_D = +10{\cdot}60$	Guye and Chavanne, *C. r.* **116**, 1454 (1893).
Iso- ,, ,,	,, $= +10{\cdot}48$	

N-propyl glycerate	,,	= −12·94	Frankland and MacGregor, *J. C. S.* **63**, 524 (1893).
Iso- ,, ,,	,,	= −11·82	
N-butyl ,,	,,	= −11·02	,,
Iso- ,, ,,	,,	= −14·23	
Sec. ,, ,,	,,	= −10·58	
N-propyl malate	,,	= −11·62	Walden, *Zt. ph. Chem.* **17**, 245 (1895).
Iso- ,, ,	,,	= −10·41	
N-propyl tartrate	,,	= +29·11	Freundler, *Ann. chim. phys.* [7] **3**, 433 (1894).
Iso- ,, ,,	,,	= +34·83	
N-butyl diacetyltartrate	,,	= + 8·0	,,
Iso- ,, ,,	,,	= +17·0	
N-butyl dipropionyltartrate	,,	= + 6·9	,,
Iso- ,, ,,	,,	= +11·4	
N-butyl dibutyryltartrate	,,	= + 6·0	,,
Iso- ,, ,,	,,	= + 8·5	

In some instances the iso-compound has a higher, in others a lower, rotatory power than the normal compound.

(*b*) *Position-Isomerism in Benzene Derivatives.*

A number of investigations have been made on the influence of the ortho, meta, and para positions of an active and an inactive, or of two active groups in disubstituted benzene compounds.

1. H. Goldschmidt and Freund[1] have determined the specific rotations of the following solids in chloroform solution the concentration *p* of which was almost exactly the same in each group.

In some cases the phenyl derivative $C_6H_5.R$, as well as the tolyl compounds $C_6H_4\langle{}^{R}_{CH_3}$, was investigated in order to determine the effect of the introduction of the CH_3 group.

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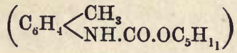
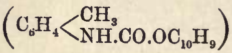
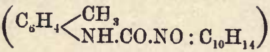
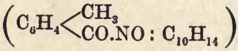
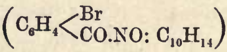
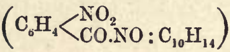
[1] Goldschmidt and Freund, *Zt. ph. Chem.* **14**, 394 (1894).

The differences δ indicate the progressive increases or decreases of the molecular rotation.

		$[\alpha]_D$	$[M]_D$	δ
I $p = 5{\cdot}3$	*l*-Amyl phenylcarbamate	+ 4·19	+ 8·7	
	" " *o*-tolylcarbamate	+ 2·66	+ 5·9	− 2·8
	" " *m*-  $\left(C_6H_4<^{CH_3}_{NH.CO.OC_5H_{11}}\right)$	+ 3·85	+ 8·5	+ 2·6
	" " *p*-	+ 4·47	+ 9·9	+ 1·4
II $p = 5{\cdot}6$	*l*-Menthyl phenylcarbamate	−77·2	−212·3	
	" " *o*-tolylcarbamate	−65·9	−190·4	−21·9
	" " *m*-  $\left(C_6H_4<^{CH_3}_{NH.CO.OC_{10}H_9}\right)$	−71·4	−206·4	+16·0
	" " *p*-	−72·3	−208·9	+ 2·5
III $p = 2{\cdot}7$	Carbanilido-*d*-carvoxime	+31·7	+ 89·9	
	Carbo-*o*-toluido "	+27·4	+ 81·7	− 8·2
	" *m*  $\left(C_6H_4<^{CH_3}_{NH.CO.NO:C_{10}H_{14}}\right)$	+29·8	+ 88·8	+ 7·1
	" *p*	+30·8	+ 91·6	+ 2·8
IV $p = 9$ to 10	Benzoyl-*d*-carvoxime	+26·6	+ 71·7	
	o-Toluyl " "	+27.1	+ 76·6	+ 5·1
	m- "  $\left(C_6H_4<^{CH_3}_{CO.NO:C_{10}H_{14}}\right)$	+26·9	+ 76·0	− 0·6
	p- "	+23·4	+ 66·3	− 9·7
V $p = 5{\cdot}5$	*o*-Bromobenzoyl-*d*-carvoxime	+26·0	+ 90·3	
	m- "  $\left(C_6H_4<^{Br}_{CO.NO:C_{10}H_{14}}\right)$	+18·2	+ 63·5	−26·8
	p- "	+14·9	+ 51·9	−11·6
VI $p = 4{\cdot}6$	*o*-Nitrobenzoyl-*d*-carvoxime	inactive		
	m- "  $\left(C_6H_4<^{NO_2}_{CO.NO:C_{10}H_{14}}\right)$	+20·7	+ 64·9	
	p- "	+17·3	+ 54·4	−10·5

From these results we see that in groups I., II., and III. the rotation increases from the *o*- compound through the *meta*- to the *para*-; in groups IV., V., and VI. the rotation decreases in that series.

[Frankland[1] predicts from theoretical reasons that the influence of the phenyl and tolyl groups should be in the order para > meta > phenyl > orthotolyl—or the reverse. The position of the phenyl derivative, however, is more often between the para- and metatolyl compounds than between the meta- and ortho-.]

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[1] Frankland and Wharton, *J. C. S.* **69**, 1584 (1896).

In groups I., II., and III. the introduction of the methyl group [in the ortho-position] causes a decrease of the activity, but an increase in IV.

2. The following acidyl tartaric esters have been investigated:

(*a*) The methyl and ethyl esters of dibenzoyl and ditoluyltartaric acids in the fused state at different temperatures. Frankland and Wharton.[1]

Methyl esters:	Temp. 100°	δ	137°	δ	183°	δ
Benzoyl $[\alpha]_D$ =	− 72·6		−66·8		−58·9	
o Toluyl ,, =	− 68·0	− 4·6	−61·7	− 5·1	−52·8	− 6·1
m- ,, ,, =	− 79·0	11·0	−70·6	8·9	−61·0	8·2
p- ,, ,, =	−102·8	23·8	−91·5	20·9	−76·9	15·9
Ethyl esters:						
Benzoyl $[\alpha]_D$ =	− 60·8		−56·7		−51·7	
o-Toluyl ,, =	− 54·7	− 6·1	−50·4	− 6·3	—	
m- ,, ,, =	− 63·7	9·0	−58·7	8·3	—	
p- ,, ,, =	− 90·0	26·3	−81·5	22·8	−69·5	

Here the rotation increases in the order *o*-, *m*-, *p*-, and the differences between the *o*- and *m*- are smaller than between the *m*- and *p*-. This holds for all temperatures. [In both series the position of the benzoyl derivative is between the ortho- and metatoluyl derivatives.]

[(*b*) The ethyl esters of monobenzoyl and the monotoluyl-tartaric acids in the fused state at different temperatures. Frankland and McCrae.[1]

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[1] Frankland and Wharton, *J. C. S.* **69**, 1309, 1583 (1896).

		Temp. 20°	δ	100°	δ	136°	δ	180°
Benzoyl	$[\alpha]_D$	= +20·9		+17·7		+16·4		—
			−9·1		−6·8		−5·8	
o-Toluyl	„	= +11·8		+10·9		+10·6		—
			1·8		1·5		1·3	
m- „	„	= +13·6		+12·6		+11·9		—
			6·0		3·2		2·5	
p- „	„	= +19·6[2]		+15·8		+14·6		+13·4

In this case the rotation increases in the order *o*-, *m*-, *p*-, but the activity of the benzoyl derivative is greater than that of any of the toluyl derivatives.

Diethyl tartaric ester has the rotation $[\alpha]_D^{20} = +7{\cdot}66$, and this increases with rise of temperature to $[\alpha]_D^{100} = +13{\cdot}59$. On the introduction of two acidyl groups (benzoyl or toluyl) the laevorotation passes into a dextro one, which decreases as the temperature rises. On the introduction of a single acidyl group the dextrorotation is retained, but is converted into one which decreases as the temperature rises. The dextrorotation at 100° of diethyl tartrate is increased by the introduction of a benzoyl or paratoluyl group, but is diminished by an ortho- or metatoluyl group. This last statement does not hold for other temperatures.

3. Methyl and ethyl esters of benzoyl and toluylmalic acids. Frankland and Wharton.[3]

Methyl esters:		Temp. 21°		100°		136°	
Benzoyl	$[\alpha]_D$	= −5·6		−11·6		−13·6	
			3·3		0·8		0.5
o Toluyl	„	= −8·9		−12·4		−14·1	
			−2·3		−0·7		−0·6
m- „	„	= −6·3		−11·7		−13·5	
			−3·1		−3·4		−3·4
p- „	„	= −3·2		− 8·3		−10·1	

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[1] Frankland and McCrae, *J. C. S.* 73, 307 (1898). [2] Calculated.

[3] Frankland and Wharton, *J. C. S.* 75, 337 (1899).

Ethyl esters:		Temp. 21°		100°		135°	
Benzoyl	$[\alpha]_D$	= −3·9		−9·8		−12·1	
o-Toluyl	„	= −6·2	2·3	−10·4	0·6	−12·0	−0·1
m- „	„	= −4·7	−1·5	−9·9	−0·5	−11·7	−0·3
p- „	„	= −0·2	−4·5	−5·5	−4·4	−7·3	−4·4

The rotation of the malic esters from which these compounds were prepared was:

Methyl . . . . . $[\alpha]_D^{20} = -6·84°$
Ethyl . . . . . $[\alpha]_D^{20} = -10·44°$

The influence of the introduction of the acidyl group is greatest in causing a decrease of the lævo-rotation of the ester in the case of paratoluyl; metatoluyl has a lesser effect, and orthotoluyl the least of all.

4. Methyl and ethyl esters of dibenzoylglyceric acid (Frankland and MacGregor[1]) and ditoluylglyceric acids. Frankland and Aston.[2]

Methyl esters:		Temp. 20°		100°		140°	
Benzoyl	$[\alpha]_D$	= +26·7		+17·4		—	
o-Toluyl	„	= +20·2	−6·5	+13·1	−4·3	+9·6	
m- „	„	= +26·4	6·2	+16·4	3·3	+11·5	1·9
p- „	„	= +41·2	14·8	+25·1	8·7	+18·5	7·0
Ethyl esters:							
Benzoyl	„	= +26·1		+18·0		—	
o-Toluyl	„	= +21·6	−4·5	+13·8	−4·2	+9·8	
m- „	„	= +26·9	5·3	+17·4	3·6	+11·9	2·1
p- „	„	= +42·4	15·5	+26·2	8·8	+18·2	6·3

Methyl-glycerate. $[\alpha]_D^{20} = -5°$ $[\alpha]_D^{100} = -8·3°$ (calculated).
Ethyl „ . „ $= -9·4$ „ $= -12·5$ „

In this case the order of the influence of the acidyl groups is: paratoluyl > metatoluyl ≷ benzoyl > orthotoluyl.

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[1] Frankland and MacGregor, *J. C. S.* 69, 104 (1896).

[2] Frankland and Aston, *J. C. S.* 75, 493 (1899).

5. β-Methyladipanilide and toluides in acetic acid solution. The concentrations are given in the column *c*. Rawitzer,[1] Guye.[2]

β-Methyladip-anilide . .	$c = 1·76$	$[\alpha]_D = +25·9$
" " *o*-toluide . .	" $= 0·35$	" $= +58·2$
" " *m*- " . .	" $= 1·52$	" $= +11·0$
" " *p*- " . .	" $= 1·57$	" $= +35·9$

6. Amyl benzoate and toluates in the liquid state. Guye and Chavanne.[3]

Amyl benzoate	$[\alpha]_D = 4·96$
" *o*-toluate	" $= 4·55$
" *m*- "	" = —
" *p*- "	" $= 5·20$

7. Menthyl benzoate and toluates in the liquid state. Tchúgaeff.[4]

Menthyl benzoate . . .	$[\alpha]_D = 90·9$
" *o*-toluate . . .	" $= 84·4$
" *m*- " . . .	" $= 87·9$
" *p*- " . . .	" $= 92·1$

8. The phenyl and tolyl amyl oxides in the liquid state. Welt.[5]

Phenyl amyl oxide . . .	$[\alpha]_D = 4·01$
o-Tolyl " " . . .	" $= 3·86$
m- " " " . . .	" $= 3·93$
p- " " " . . .	" $= 4·26$

9. Binz[6] derived the following specific rotations from solutions in chloroform:

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[1] Rawitzer, *Thesis*, Zurich, 1896, 25.

[2] Guye, *Bull.* [3] 15, 1158 (1896).

[3] Guye and Chavanne, *Bull.* [3] 15, 298 (1896).

[4] Tchúgaeff, *Ber.* 31, 1775 (1898).

[5] Welt, *Ann. chim. phys.* [7], 6, 142 (1895).

[6] Binz, *Zt. ph. Chem.* 12, 727 (1893).

		$[\alpha]_D$	
o-Oxybenzylidene fenchylamine	$(p=2{\cdot}5)$	66·0	6·0
p- „ $\left(C_6H_4<\genfrac{}{}{0pt}{}{OH}{CH:N.C_{10}H_{17}}\right)$	$(p=1{\cdot}3)$	72·0	
o-Methoxybenzylidene fenchylamine	$(p=5)$	59·4	18·7
p- „ $\left(C_6H_4<\genfrac{}{}{0pt}{}{OCH_3}{CH:N.C_{10}H_{17}}\right)$	$(p=5)$	78·1	

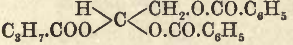
10. Maldianilide and malditoluides in solution in glacial acetic acid. Walden.[1]

Maldianilide $(c=1{\cdot}5)$	$[\alpha]_D=60{\cdot}7$	
Maldi-o-toluide $(c=1)$	„ $=66{\cdot}5$	3·5
„ p- „ $(c=1)$	„ $=70{\cdot}0$	

In the majority of cases cited the para-derivative has a higher rotation than the ortho-, and the meta- takes an intermediate position.

Cases are known of isomeric compounds prepared from the same original substance having opposite rotatory powers. Thus Frankland and MacGregor[2] found:

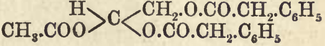
Propyldibenzoylglycerate



$$\genfrac{}{}{0pt}{}{H}{C_3H_7.COO}>C<\genfrac{}{}{0pt}{}{CH_2.O.CO.C_6H_5}{O.CO.C_6H_5}$$

$[\alpha]_D^{15}=+21{\cdot}0°.$

Methyldiphenacetylglycerate



$$\genfrac{}{}{0pt}{}{H}{CH_3.COO}>C<\genfrac{}{}{0pt}{}{CH_2.O.CO.CH_2.C_6H_5}{O.CO.CH_2.C_6H_5}$$

$[\alpha]_D^{15}=-16{\cdot}1°.$

Carnelutti and Nasini[3] found the following rotations in chloroform solution for the isomers of the santonin group:

Santonin	$[\alpha]_D=-171{\cdot}4°$
Metasantonin	„ $=+118{\cdot}8°$
Santonid	„ $=+744{\cdot}6°$
Metansantonid	„ $=-223{\cdot}5°$
Parasantonid	„ $=+897{\cdot}3°$

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[1] Walden, *Zt. ph. Chem.* **17**, 265 (1895).

[2] Frankland and MacGregor, *J. C. S.* **69**, 104 (1896).

[3] Carnelutti and Nasini, *Ber.* **13**, 2208 (1880).

(*c*) *Stereoisomeric Compounds.*

Walden[1] has made a series of observations on the active amyl esters of fumaric and maleic acids and their derivatives. For their preparation *l*-amyl alcohol was used.

Diamyl ester of:	$[\alpha]_D$	$[M]_D$	Diff. in $[M]_D$ F−M
fumaric acid	+5·93	+15·17	+3·35
maleic acid	+4·62	+11·82	
chlorofumaric acid	+5·78	+16·78	+5·08
chloromaleic acid	+4·03	+11·70	
bromofumaric acid	+5·99	+20·07	+4·71
bromomaleic acid	+4·58	+15·36	
methylfumaric (mesaconic) acid	+5·93	+16·01	+4·84
methylmaleic (citraconic) acid	+4·14	+11·17	
		Average:	4·50

The mean difference in $[M]_D$ of these compounds is 4·5—the fumaroid form having the greater rotation.

When we come to compounds having a close connection with these but which are saturated (succinic acid series), then, as Walden has shown, the above rule does not hold.

Diamyl ester of	$[\alpha]_D$	$[M]_D$	Diff. in $[M]_D$ F−M
p- dimethylsuccinic acid	+3·66	+10·47	+0·68
anti- ,, ,,	+3·42	+ 9·79	
racemic acid	+3·37	+ 9·77	+4·06
mesotartaric acid	+4·77	+13·83	

It must be noted, however, that a racemic acid ester of active amyl alcohol does not really exist. The substance used was a mixture of the amyl esters of *d*- and *l*-tartaric acids, and as these are not mirror-images of each other, they do not give a true racemic compound.

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[1] Walden, *Zt. ph. Chem.* **20**, 377 (1896).

[As illustrating the influence of the replacement of hydrogen by chlorine in the acetylglycerates the results obtained by Frankland and Patterson[1] may be introduced here.

	Methyl			Ethyl		
	$[\alpha]_D^{15}$	$[M]_D^{15}$	δ	$[\alpha]_D^{15}$	$[M]_D^{15}$	δ
Glycerate	− 4°·80	− 5°·76		− 9°·18	−12°·30	
Diacetylglycerate	−12·04	−24·56		−16·31	−35·55	
Di-monochloracetylglycerate	−12·91	−35·24	10·68	−16·80	−48·22	12·67
Di-dichloracetylglycerate	−13·96	−47·74	12·5	−18·20	−64·79	16·57
Di-trichloracetylglycerate	−14·2	−58·36	10·62	−18·7	−79·47	14·68

The substitution by the second two chlorine atoms evidently produces a slightly greater effect on the molecular rotation than either of the other substitutions.]

24. Homologous Series. — The relationship which exists in these series can be seen from the following observations:

Change of Molecular Rotation with Increase of CH_2.

	$[\alpha]_D$	$[M]_D$	Diff.
1. Amyl formate	+2·01	+2·33	
,, acetate	+2·53	+3·29	+0·96
,, propionate	+2·77	+3·99	+0·70
,, *n*-butyrate	+2·69	+4·25	+0·26
,, *n*-valerate	+2·52	+4·33	+0·08
,, *n*-caproate	+2·40	+4·46	+0·13
,, *n*-heptate	+2·21	+4·42	−0·04
,, *n*-caprate	+2·10	+4·49	+0·07
,, *n*-nonate	+1·95	+4·44	−0·05
,, laurate	+1·56	+4·21	
,, palmitate	+1·28	+4·17	
,, stearate	+1·27	+4·49	

Guye and Chavanne, *C.r.* **120**, 452 (1895); *Bull.* [3] **15**, 275 (1896).

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[1] Frankland and Patterson, *J. C. S.* **73**, 181 (1898).

	$[\alpha]_D$	$[M]_D$	Diff.
2. Menthol	−50·0	− 78·0	
Menthyl formate	−79·52	−146·3	+68·3
,, acetate	−79·42	−157·3	+11·0
,, propionate	−75·51	−160·2	+ 2·9
,, *n*-butyrate	−69·52	−156·9	− 4·3
,, *n*-valerate	−65·55	−157·3	+ 0·4
,, *n*-caproate	−62·07	−157·7	+ 0·4
,, *n*-heptate	−58·85	−157·7	0
,, *n*-caprate	−55·25	−155·8	− 1·9

Tchúgaeff, *Ber.* **31**, 364 (1898).

3. Valeric acid	+13·64	+13·91	
Methyl valerate	+16·83	+19·53	+5·62
Ethyl ,,	+13·44	+17·47	−2·06
n-Propyl ,,	+11·68	+16·82	−0·65
n-Butyl ,,	+10·60	+16·75	−0·07

Guye and Chavanne, *C. r.* **116**, 1454 (1893).

4. Methyl glycerate	− 4·80	− 5·76	
Ethyl ,,	− 9·18	−12·30	+6·54
n-Propyl ,,	−12·94	−19·15	+6·85
n-Butyl ,,	−13·19	−21·37	+2·22
Heptyl ,,	−11·30	−23·05	
Octyl ,,	−10·22	−22·28	−0·77

Frankland and MacGregor, *J. C. S.* **63**, 1415 (1893).

5. Methyl diacetylglycerate	−12·04	−24·56	
Ethyl ,,	−16·31	−35·56	+11·00
n-Propyl ,,	−19·47	−45·17	+ 9·61

Frankland and MacGregor, *J. C. S.* **63**, 1430 (1893).

Methyl dibenzoylglycerate	+26·89	+88·20	
Ethyl ,,	+26·58	+90·90	+ 2·70
n-Propyl ,,	+21·00	+74·76	−16·14

Frankland and MacGregor, *J. C. S.* **69**, 104 (1896).

	$[\alpha]_D$		
	I.	II.	III.
Methyl malate	− 6·85	− 6·88	− 7·34
Ethyl ,,	−10·18	−10·65	−12·42
n-Propyl ,,	−11·62	−11·60	−13·70
n-Butyl ,,	—	−10·72	−12·20
Amyl ,,	− 9·92	—	—
Capryl ,,	− 6·92	—	—

	$[M]_D$:	δ		δ		δ
Methyl malate .	−11·10		−11·15		−11·89	
Ethyl ,, .	−19·35	+8·25	−20·23	+9·08	−23·56	+11·67
n-Propyl ,, .	−25·32	+5·97	−25·29	+5·06	−29·87	+ 6·31
n-Butyl ,, .	—		−26·38	+1·09	−30·01	+ 0·14
Amyl ,, .	−27·19		—	—	—	
Capryl ,, .	−24·77	−2·42	—	—	—	

I. Prepared by esterifying the acid and alcohol by means of sulphuric acid. Walden, *Zt. ph. Chem.* **17**, 245 (1895).

II. Preparation as in I. Anschütz and Reitter, *Zt. ph Chem.* **16**, 493 (1895).

III. Prepared by the action of alkyl iodides on silver malate. Purdie and Williamson, *J. C. S.* **69**, 818 (1896).

8. Diacetyl malate of	$[\alpha]_D$		$[M]_D$			
	I.	II.	I.	δ	II.	δ
Methyl . .	−22·92	−22·86	−46·76		−46·64	
Ethyl . .	−22·52	−22·60	−52·25	+5·49	−52·43	+5·79
n-Propyl .	−22·85	−22·68	−59·40	+7·15	−58·96	+6·33
n-Butyl .	−21·88	−19·93	−63·01	+3·61	−57·38	−1·58

I. Walden, *Zt. ph. Chem.* **17**, 245 (1895).

II. Anschütz and Reitter, *Zt. ph. Chem.* **16**, 493 (1895).

	$[\alpha]_D$	$[M]_D$	Diff. δ
9. Methyl *d*-tartrate	+ 2·14	+ 3·8	
Ethyl ,, ...	+ 7·66	+15·7	+11·9
n-Propyl ,, ...	+12·44	+29·0	+13·3

Pictet, *Arch. phys. nat.* [3] **7**, 82 (1882).

	$[\alpha]_D$	$[M]_D$	δ
10. Methyl chlorosuccinate . . .	+41·42	+74·8	
Ethyl ,, ...	+27·50	+57·3	−17·5
n-Propyl ,, ...	+25·63	+60·6	+ 3·3
n-Butyl ,, ...	+21·57	+57·1	− 3·5
Amyl ,, ...	+21·56	+63·1 (2 act. rad.)	

Walden, *Zt. ph. Chem.* **17**, 245 (1895).

11.	Santoic acid	− 70·31	−185·6	
	Methyl santoate	− 52·33	−145·5	−40·1
	Ethyl ,,	− 45·35	−132·4	−13·1
	n-Propyl ,,	− 39·34	−120·4	−12·0
	Parasantoic acid	− 89·51	−260·1	
	Methyl parasantoate	−108·91	−302·8	+42·7
	Ethyl ,,	− 99·98	−291·9	−10·9
	n-Propyl ,,	− 91·27	−279·3	−12·6

The rotations are calculated from observations carried out with chloroform solutions. Carnelutti and Nasini, *Ber.* **13**, 2208 (1881).

12.	Fenchylamine (liquid)		−24·89	− 38·0	
	Formyl-fenchylamine	$(p=3{\cdot}9)$	−36·56	− 66·0	
	Acetyl ,,	$(p=4{\cdot}6)$	−46·62	− 90·7	+24·7
	Propionyl ,,	$(p=5{\cdot}0)$	−53·16	−110·9	+20·2
	Butyryl ,,	$(p=1{\cdot}8)$	−53·11	−118·2	+ 7·3

The observations were made with chloroform solutions. Binz, *Zt. ph. Chem.* **12**, 731 (1893).

From a comparison of the molecular rotations, [M], in the above tables we see that:

In the homologous esters the value of [M] sometimes increases, and in other cases decreases with rising molecular weight.

An increase occurs with the amyl esters of the fatty acids (No. 1), the menthyl esters of the fatty acids (No. 2), the alkyl esters of glyceric and diacetylglyceric acids (Nos. 4 and 5), and the acidyl-fenchylamines (No. 12). It is generally found that the increase of the molecular rotation is greatest between the first and second members of the series, and after that it continuously diminishes. The differences for CH_2 in the higher members of the series are very small, and, indeed, sometimes negative (Nos. 1, 2, 4, 8).

On this account Tchúgaeff[1] suggests that for each series the molecular rotation becomes constant at a certain member, and remains so in the higher members, or at least suffers only very small variations. A maximum value of the molecular rotation has been found with the amyl and menthyl esters of the fatty acids.

Decrease in the value of [M] takes place in the series of esters of valeric acid (No. 3), santoic and parasantoic acids (No. 11). In the latter cases the decreases are very considerable.

No regularity has been observed with the esters of dibenzoylglyceric acid (No. 6), and of chlorosuccinic acid (No. 10).

The greatest change in the molecular rotation occurs when an active alcohol or an active acid is converted into the formyl or methyl ester (Nos. 2, 3, and 11).

[Frankland[2] points out that as the series of esters of malic and lactic acids are ascended, a maximum followed by a diminution in the molecular rotation is reached, and this is reasonably explicable as due to the association of the initial terms.

The same phenomenon is exhibited by the esters of tartaric, glyceric, and diacetylglyceric acids, but the maximum is too pronounced to be accounted for by association.]

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[1] Tchúgeaff, *Ber.* 31, 360 (1898).

[[2] Frankland, *J. C. S.* 75, 366 (1899).]

25. Influence of the Mode of Linkage of the Carbon Atoms.

(*a*) *Transformation of a Single to a Double Linkage by Elimination of Two Atoms of Hydrogen.*

The change of rotation which occurs on this transformation has been studied by Walden[1] in a series of liquid esters of active amyl

$$CH(CH_3)(C_2H_5)-(CH_2)-$$

alcohol. The compounds were prepared from lævorotatory amyl alcohol.

	$C_5H_{11}=A$	$[\alpha]_D$	$[M]_D$	Diff.
Amyl *n*-butyrate	$CH_3-CH_2-CH_2-CO_2A$	+2·81	+ 4·43	2·19
„ crotonate	$CH_3-CH=CH-CO_2A$	+4·24	+ 6·62	
„ isobutyrate	$CH_3-\underset{\underset{CH_3}{\vert}}{CH}-CO_2A$	+3·10	+ 4·90	0·57
„ methacrylate	$CH_2=\underset{\underset{CH_3}{\vert}}{C}-CO_2A$	+3·51	+ 5·47	
Diamyl succinate	$\begin{array}{l}CH_2-CO_2A\\ \vert\\ CH_2-CO_2A\end{array}$	+3·76	+ 9·71	5·46
„ fumarate	$\begin{array}{l}CH-CO_2A\\ \Vert\\ CH-CO_2A\end{array}$	+5·93	+15·17	
„ chlorosuccinate	$\begin{array}{l}CH_2-CO_2A\\ \vert\\ CHCl-CO_2A\end{array}$	+3·75	+10·98	5·80
„ chlorofumarate	$\begin{array}{l}CH-CO_2A\\ \Vert\\ CCl-CO_2A\end{array}$	+5·78	+16·78	

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[1] Walden, *Zt. ph. Chem.* **20**, 569 (1896).

		$[\alpha]_D$	$[M]_D$	Diff.
Diamyl methylsuccinate	$\begin{array}{l} CH_2-CO_2A \\ \vert \\ CH.CH_3-CO_2A \end{array}$	$+3{\cdot}76$	$+\ 9{\cdot}99$	6·02
,, mesaconate	$\begin{array}{l} CH-CO_2A \\ \Vert \\ C.CH_3-CO_2A \end{array}$	$+5{\cdot}93$	$+16{\cdot}01$	
Triamyl tricarballylate	$\begin{array}{l} CH_2-CO_2A \\ \vert \\ CH-CO_2A \\ \vert \\ CH_2-CO_2A \end{array}$	$+4{\cdot}01$	$+15{\cdot}48$	8·18
,, aconitate	$\begin{array}{l} CH-CO_2A \\ \Vert \\ C-CO_2A \\ \vert \\ CH_2-CO_2A \end{array}$	$+6{\cdot}16$	$+23{\cdot}66$	
Amyl hydrocinnamate	$C_6H_5-CH_2-CH_2-CO_2A$	$+2{\cdot}26$	$+\ 4{\cdot}98$	11·38
,, cinnamate	$C_6H_5-CH=CH-CO_2A$	$+7{\cdot}51$	$+16{\cdot}36$	

It has been found in every case that the transformation of a single into a double carbon atom linkage is accompanied by an increase in the rotatory power of the substance.

(*b*) *Transformation of a Double into a Triple Carbon Atom Linkage.*

Only one example of this case has been investigated, and that by Walden:[1]

		$[\alpha]_D$	$[M]_D$	Diff.
Amyl cinnamate	$C_6H_5-CH=CH-CO_2A$	$+7{\cdot}51$	$+16{\cdot}36$	$-4{\cdot}31$
,, phenylpropiolate	$C_6H_5-C\equiv C-CO_2A$	$+5{\cdot}58$	$+12{\cdot}05$	

Here a diminution in the activity takes place.

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[1] Walden, *Zt. ph. Chem.* **20**, 569 (1896).

(c) *Transformation of a Chain Carbon Compound into a Cyclic one.*

Van't Hoff[1] first called attention to the very considerable influence which a ring formation exerts on the degree of rotation—so considerable, in fact, that it may occasion a change of sign.

Exact numerical data are difficult to obtain, as most of the compounds which can be used in the investigation of this question are solid, and their specific rotation varies with the solvent used and with the concentration. The influence of the ring formation is shown by the two following examples of dicarboxylic acids and their anhydrides:

Diacetyl-tartaric acid	Water	$c=17\cdot95$	$[\alpha]_D = -\ 23\cdot0°$
	,,	$c=3\cdot76$	,, $= -\ 19\cdot3$
	Ethyl alcohol	$c=7\cdot37$	,, $= -\ 23\cdot6$
	,, ,,	$c=3\cdot27$	,, $= -\ 21\cdot5$
Diacetyl-tartaric anhydride	Acetone	$c=11\cdot66$	,, $= +\ 59\cdot7$
	,,	$c=4\cdot40$	,, $= +\ 62\cdot0$
	Benzene	$c=2\cdot09$	,, $= +\ 58\cdot7$
	,,	$c=1\cdot05$	,, $= +\ 63\cdot1$
Dibenzoyl-tartaric acid (anhydrous)	Ethyl alcohol	$c=4\cdot76$	,, $= -117\cdot7$
	Methyl ,,	$c=4\cdot63$	,, $= -122\cdot1$
Dibenzoyl-tartaric anhydride	Acetone	$c=4\cdot64$	,, $= +142\cdot9$

Pictet, *Jahresberichte*, 1882, 856.

In both cases the rotation of the anhydride is greater than that of the acid and in the opposite direction.

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[1] Van't Hoff, *Die Lagerung der Atome im Raume*, 1894, p. 109.

A different behaviour is shown by the following compounds:

Chlorosuccinic acid	Acetic ether	. $c = 10$	$[\alpha]_D = +52{\cdot}7°$
	„	. $c = 6{\cdot}6$	„ $= +52{\cdot}9$
Chlorosuccinic anhydride	„	. $c = 10$	„ $= +30{\cdot}9$
	„	. $c = 5$	„ $= +33{\cdot}6$

Walden, *Zt. ph. Chem.*, **17**, 245 (1895).

The rotation of the anhydride is smaller than that of the acid, and of the same direction.[1]

The activity of the lactones of the acids of the sugar group is always much greater than that of the acids themselves. As the true rotatory power of the acids cannot be exactly determined on account of the multirotation which takes place, Alberda van Ekenstein, Jorissen, and Reicher[2] have investigated the alkali salts with which no change of rotation occurs, and which give the rotation of the active acid ion. The lactones were polarimetrically examined immediately on being dissolved, in order as much as possible to avoid the effects of multirotation. The concentration of the solutions employed was 2 to 6·5 grams of acid ion, and 4 to 10 grams of lactone per 100 c.c. The following table[3] is given by the

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[1] Chlorosuccinic acid dissolved in water has a much lower rotation than when dissolved in acetic ether. Walden, *Ber.* **26**, 215 (1893), gives the following data:

Chlorosuccinic acid	Water .	. $c = 16$	$[\alpha]_D = +20{\cdot}6$
	„ .	. $c = 6{\cdot}4$	„ $= +20{\cdot}8$
	„ .	. $c = 3{\cdot}2$	„ $= +21{\cdot}3$

[2] Alberda van Ekenstein, Jorissen, and Reicher, *Zt. ph. Chem.* **21**, 383 (1896).

[3] The table contains the mean values of the data given in the original paper.

observers mentioned, and includes results obtained by Fischer, Tollens, and others :

	$[M]_D$		Change of rotation
	acid ion	lactone	
Ribonic acid	+ 2°	− 30°	32°
d-Gluconic acid	+ 16	+ 116	100
l-Mannonic acid	+ 20	− 97	117
d-Gulonic acid	− 27	+ 99	126
l-Gulonic acid	+ 27	− 99	126
Saccharonic acid	− 11	+ 152	163
Isosaccharonic acid	− 11	+ 102	113
d-Saccharic acid	+ 26	+ 77	51[1]
Mannosaccharic acid	+ 2	+ 354[2]	352
α-Rhamnohexonic acid	+ 13	+ 163	150
α-Glucoheptonic acid	+ 16	− 112	128

The rotatory power of the cyclic lactones is in every case much greater than that of the acid ion, and often in the opposite direction. The change of rotation is generally between 100 and 150 degrees; no regularity, however, can be recognised.

In the case of carbocyclic and heterocyclic compounds the value of the rotation is generally very high, especially when the compound contains several asymmetric carbon atoms, as has been found with the members of the santonin group, and with the alkaloids :

		$[\alpha]_D$
Limonene α-nitrosochloride	in chloroform	± 314°
„ β- „	„ „	± 241
Sodium nitro-camphor	„ water	+ 233
Metasantonid	„ chloroform	− 224
Santonid	„ „	+ 754
Parasantonid	„ „	+ 892
Conchinine	„ alcohol	+ 255
Thebaine	„ „	− 219
Cupreine sulphate	„ water	− 290

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[1] [In the original paper the difference given is obviously erroneous.]

[2] Calculated for the double lactone $C_6H_6O_6$.

On the other hand, certain cyclic compounds have a comparatively low rotation, as, for instance:

		$[\alpha]_D$
Tetrahydronaphthalene-diamine hydrochloride	in water	− 7·5
Benzoylhydrochlorocarvoxime	,, acetic ether	+ 9·9
Aconitine	,, alcohol	+ 11·0
Cinchonicine	,, water	+ 28·7
Cocaine	,, chloroform	− 16·3
Conine	liquid	+ 18·3

And some non-cyclic compounds possess a very high rotation:

		$[\alpha]_D$
Cystine	in hydrochloric acid	205·9
α- Phenylchloracetyl chloride	,, carbon disulphide	158·3

26. Summation of the Rotatory Actions of several Asymmetric Groups. Optical Superposition.—Van't Hoff,[1] when he first brought forward the doctrine of the asymmetric carbon atom, made the assumption that in compounds which contain several such atoms, one asymmetric group does not alter the optical effect of any of the others; consequently, the rotatory power of the compound will be equal to the sum or difference of the rotatory effects of each asymmetric group present, according as these are of the same or opposite sign.

The correctness of this supposition, which forms the basis of all considerations on optical isomerism, has recently been experimentally proved by Guye and by Walden. These investigators examined isomeric liquid amyl esters prepared from active and inactive material in the following three combinations:

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[1] Van't Hoff, *Bull.* [2], 23, 298 (1875); *Die Lagerung der Atome im Raume*, 1877, p. 37; 1894, p. 120.

I. Inactive alcohol and active acid.
II. Active „ „ inactive acid.
III. „ „ „ active acid.

The ester III. contains the two asymmetric groups of I. and II., and therefore the sum of the specific rotations of I. and II. should be equal to that of III.

As the following table shows, this is actually the case. In the preparation of the esters from inactive acid, or from inactive amyl alcohol, the racemic form of these compounds was used.

Amyl lactates:

I.	*i*-amyl *l*-lactate	$[\alpha]_D$ = −6·38°
II.	*l*- „ *i*- „	„ = +2·64
III.	*l*- „ *l*- „	„ = −3·93
		I. + II. = −3·74

Walden, *Zt. ph. Chem.* **17**, 721 (1895).

Amyl valerates:

I.	*i*-amyl *d*-valerate	$[\alpha]_D$ for $l = 0·5$ dm. +4·40°
II.	*l*- „ *i*- „	„ „ „ „ +1·22
III.	*l*- „ *d*- „	„ „ „ „ +5·32
		I. + II. = +5·62

Guye and Gautier, *C. r.* **119**, 953 (1894).

Amyl *a*-oxybutyrates:

I.	*i*-amyl *l*-oxybutyrate	$[\alpha]_D$ = −8·5°
II.	*l*- „ *i*- „	„ = +1·5
III.	*l*- „ *l*- „	„ = −7·3
		I. + II. = −7·0

Guye and Jordan, *C. r.* **120**, 632 (1895).

Amyl amylacetates:

I. *i*-amyl *d*-amylacetate . . . . . $[\alpha]_D$ = +4·36°
II. *l*- „ *i*- „ . . . . . „ = +1·54
III. *l*- „ *d*- „ . . . . . „ = +5·64
I. + II. = +5·90

Guye, *C. r.* **121**, 827 (1895).

Amyl phenyl-chloracetates:

I. *i*-amyl *d*-phenyl-chloracetate . . . $[\alpha]_D$ = +23·31°
II. *l*- „ *i*- „ . . . „ = + 3·23
III. *l*- „ *d*- „ . . . „ = +26·79
I. + II. = +26·54

Walden, *Zt. ph. Chem.* **17**, 722 (1895).

Amyl mandelates:

I. *i*-amyl *l*-mandelate . . . . . $[\alpha]_D$ = −96·46°
II. *l*- „ *i*- „ . . . . . . „ = + 2·76
III. *l*- „ *l*- „ . . . . . . „ = −94·02
I. + II. = −93·70

Walden, *Zt. ph. Chem.* **17**, 721 (1895).

Diamyl chlorosuccinates:

I. *i*-amyl *d*-chlorosuccinate . . . $[\alpha]_D$ = +21·56°
II. *l*- „ *i*- „ . . . „ = + 3·75
III. *l*- „ *d*- „ . . . „ = +25·15
I. + II. = +25·31

Walden, *Zt. ph. Chem.* **17**, 723 (1895).

Diamyl amylmalonates:

I. *i*-amyl *d*-amylmalonate . . . . $[\alpha]_D$ = +6·10°
II. *l*- „ *i*- „ . . . . . „ = +3·48
III. *l*- „ *d*- „ . . . . . „ = +9·65
I. + II. = +9·58

Guye, *C. r.* **121**, 827 (1895).

Diamyl malates:

I. *i*-amyl *l*-malate	$[\alpha]_D =$ −9·92°
II. *l*- „ *i*- „	„ = +3·50
III. *l*- „ *l*- „	„ = −6·88
	I. + II. = −6·42

Walden, *Zt. ph. Chem.* **17**, 722 (1895).

Diamyl tartrates:

	(*a*)	(*b*)
I. *i*-amyl *d*-tartrate	$[\alpha]_D =$ +14·10°	+14·67°
II. *l*- „ *i*- „	„ = + 3·37	+ 3·38
III. *l*- „ *d*- „	„ = +17·73	+18·61
I. + II.	= +17·47	+18·05

(*a*) Walden, *Zt. ph. Chem.* **17**, 723 (1895).
(*b*) Guye, *C. r.* **122**, 932 (1896).

Diamyl divaleryltartrates (6 asymmetric carbon atoms):

	Amyl	valeryl	tartrate	$[\alpha]_D$
I.	*l*	*i*	*i*	+ 2·44°
II.	*i*	*d*	*i*	+ 3·48
III.	*i*	*i*	*d*	+ 6·42
IV.	*l*	*d*	*d*	+11·32
			I. + II. + III.	+12·34

Guye and Goudet, *C. r.* **122**, 932 (1896).

Optical superposition may be recognised by comparing the following compounds, using the molecular rotation [M] on account of the different compositions of the substances:

I. Amyl acetate	$[M]_D =$ + 3·25°
II. Amylacetic acid	„ = +11·08
III. Amyl amylacetate	„ = +14·02
	I. + II. = +14·33

Walden *Zt. ph. Chem.* **15**, 638 (1894).

The great differences which occur in the specific rotatory powers of isomeric sugars—*e.g.* the hexoses and also the hexonic acids—are evidently due, as Van't Hoff[1] suggested, to the summation of the effects of the four asymmetric groups present, whose rotatory powers are unequal and not all of the same sign.

27. Dependence of the Rotatory Power of an Active Atomic Grouping on the Masses of the Four Radicles united to the Asymmetric Carbon Atom. The Hypothesis of Guye.—An attempt to derive the degree and direction of rotation from the nature of the active molecule was simultaneously made in 1890 by Ph. A. Guye[2] and by A. Crum Brown;[3] the principle in both is founded on the tetrahedral form of the asymmetric group and the relative masses of the four radicles. The problem, which was most thoroughly studied and brought into mathematical form by Guye,[4] was well calculated to excite interest, and it has given a stimulus to many researches.

The general form in which Guye[5] brought forward the hypothesis in 1893 is as follows:

---

[1] Van't Hoff, *Die Lagerung der Atome im Raume*, 1894, p. 120.

[2] Guye, first paper: *C. r.* **110**, 714 (1890).

[3] Crum Brown, *Proc. R. Soc. Edin.* **17**, 181 (1890).

[4] Guye, *C. r.* **111**, 745 (1891); **114**, 473 (1892); **116**, 1133, 1378, 1451, 1454 (1893); **119**, 906 (1894); **120**, 157, 452, 632, 1274 (1895); *Thesis*, Paris (1895); *Conférences de la Soc. chim.*, Paris, 1891, 149; *Arch. phys. nat.* [3], **26**, 97, 201, 333 (1891); *Ann. chim. phys.* [6], **25**, 145 (1892); *Bull.* [3], **9**, 403 (1893).

[5] Guye, *C. r.* **116**, 1378, 1451 (1893).

The so-called *product of asymmetry* P gives a measure of the size (or degree) and sign (or direction) of the rotatory power of an active molecule. This product of asymmetry is equal to the product of the six perpendiculars from the centre of gravity of the tetrahedral model to the six planes of symmetry of the original regular tetrahedron. According to the orientation of the four radicles united to the asymmetric carbon atom P is determined in different manners.

1. If the tetrahedron is regular and the radicles are exactly at the solid angles, then the product of asymmetry is dependent only on the masses a, b, c, d, of the four groups, *i.e.* on the chemical formula-weight of the same. In this case we have for P the expression:[1]

$$\text{I. } P = \frac{(a-b)(a-c)(a-d)(b-c)(b-d)(c-d)}{(a+b+c+d)^6}(l \,.\, \sin \alpha)^6$$

and the constant factor $(l \,.\, \sin \alpha)^6$ may be omitted.[2]

2. The masses a, b, c, d may be disposed at different distances l, m, n, p from the middle point of the original tetrahedron, but always on the prolongations of the lines joining the middle point and the four solid angles.

3. The masses a, b, c, d may be disposed at different distances l, m, n, p from the centre of the original tetrahedron, and may so attract each other

---

[1] For the development of this formula, see the original paper.

[2] In this factor, l denotes the distance of the four masses from he centre of the tetrahedron, and α the angle 54° 44′.

that displacement occurs, and the lines l, m, n, p, make different angles with each of the six original planes of symmetry ($\alpha_1 \ldots\ldots \alpha_6$ for l; $\beta_1 \ldots\ldots \beta_6$ for m; $\gamma_1 \ldots\ldots \gamma_6$ for n; $\delta_1 \ldots\ldots \delta_6$ for p).

The complicated expressions[1] for P for case 2 and for the quite general case 3 cannot be solved, as they contain undeterminable quantities ($l, m, n, p, \alpha \ldots\ldots \beta \ldots\ldots \gamma \ldots\ldots \delta \ldots\ldots$). We are, therefore, restricted to formula I., and we make the assumption that the influences denoted in cases 2 and 3 are too small to give rise to appreciable disturbances.

The above equation satisfies the necessary conditions that:

(*a*) The product P must be zero when two or more of the masses a, b, c, d are equal, *i.e.* when the asymmetry of the molecule is removed.

(*b*) The product P must remain the same in value, but its sign must be changed when two of the values a, b, c, d are interchanged. Such a change corresponds to the transformation of the dextrorotatory form of a substance into the lævorotatory isomer.

The changes of the product P which take place on varying the masses a, b, c, d, must run parallel with the changes of the rotatory power. If the weights of the groups are in the order

$$a > b > c > d,$$

then when a is gradually replaced by smaller values and the original substance is, for instance, dextrorotatory, the following is to be expected:

---

[1] See the original paper.

1. So long as a remains greater than b, according to the ratio between the numbers, either a continual diminution of the dextrorotation, or at first an increase to a maximum, then a decrease, must take place.

2. $a=b$. Inactivity occurs.
3. $a<b$. Transition to an increasing lævorotation which rises to a maximum, then diminishes.
4. $a=c$. Second case of inactivity occurs.
5. $a<c$. Dextrorotation again occurs, which rises to a maximum, then diminishes.
6. $a=d$. Third case of inactivity occurs.
7. $a<d$. Increasing lævorotation occurs.

When these previsions came to be experimentally tested they appeared at first to be confirmed. Thus, in some homologous series the coincidence (perfect or approximate) of the maximum point of the rotation with a maximum point of the product of asymmetry was proved. This is seen from the table given by Guye and Chavanne[1] calculated from observations by Frankland and MacGregor[2] on the rotations of the esters of *l*-glyceric acid. The product of asymmetry P in the table is multiplied by 10^6 in order to give convenient numbers:

---

[1] Guye and Chavanne, *C. r.* **116**, 1454 (1893).

[2] Frankland and MacGregor, *J. C. S.* **63**, 524 (1893).

l-Glycerate of	*a* *C(COOR)	*b* (CH_2OH)	*c* (OH)	*d* (H)	$[\alpha]_D$	$[M]_D$	$P.10^6$
n-Butyl .	101	31	17	1	−11·02[1]	−17·9	347
n-Propyl .	87	31	17	1	−12·94	−19·2	358
Ethyl .	73	31	17	1	− 9·18	−12·3	345
Methyl .	59	31	17	1	− 4·80	− 5·8	289

In the case of the valeric acid esters investigated by Guye and Chavanne,[2] the coincidence of the maximum points is displaced by only one term:

Valerate of	*a* *C(COOR)	*b* (C_2H_5)	*c* (CH_3)	*d* (H)	$[\alpha]_D$	$[M]_D$	$P.10^6$
n-Butyl .	101	29	15	1	+10·60	+16·75	351
n-Propyl .	87	29	15	1	+11·68	+16·82	364
Ethyl .	73	29	15	1	+13·44	+17·47	374
Methyl .	59	29	15	1	+16·83	+19·53	332
Valeric acid .	45	29	15	1	+13·64	+13·91	218

The same is true of the amyl esters of the fatty acids[3] if we compare the specific rotations with the products of asymmetry:

Amyl *n*-laurate . . .	$[\alpha]_D$ = +1·56 .	$P.10^6$ = 144
„ *n*-nonate . . .	„ = +1·95 .	„ = 204
„ *n*-caprate . . .	„ = +2·10 .	„ = 229
„ *n*-heptate . . .	„ = +2·21 .	„ = 258
„ *n*-caproate . .	„ = +2·40 .	„ = 289
„ *n*-valerate . .	„ = +2·52 .	„ = 321
„ *n*-butyrate . .	„ = +2·69 .	„ = 351
„ propionate . .	„ = +2·77 .	„ = 373
„ acetate . . .	„ = +2·53 .	„ = 374
„ formate . . .	„ = +2·01 .	„ = 332

---

[1] Frankland and MacGregor afterwards (*J. C. S.* 63, 1417) gave fo *n*-butyl *l*-glycerate the corrected value $[\alpha]_D = -13·19°$, $[M]_D = -21·4°$, which renders this example unfit for the confirmation of the hypothesis.

[2] Guye and Chavanne, *C. r.* 116, 1454 (1893).

[3] Guye and Chavanne, *C. r.* 119, 906 (1894). The maximum o the molecular rotation [M] takes place at amyl caprate, *i.e.* very far removed from the maximum of the product of asymmetry.

Further investigations of these relationships, in which, besides Guye,[1] many other observers, but particularly Walden,[2] have taken part, have gradually led to our acquiring many facts which are not in agreement with the corollaries of the hypothesis. The following are the chief points of disagreement:

1. Compounds in which two of the groups *a*, *b*, *c*, *d* are of equal weight, and which accordingly should be inactive, often possess a high rotatory power. Walden[3] gives a number of instances of this kind:

a	*b*	*c*	*d*	$[\alpha]_D$	$[M]_D$
Dimethyl acetylmalate					
*C($CH_2.COOCH_3$)	($CO.OCH_3$)	($O.C_2H_3O$)	(H)	−22·9	−46·8
73	59	59	1		
Methyl acetylmandelate					
*C(C_6H_5)	($CO.OCH_3$)	($O.C_2H_3O$)	(H)	−146·4	−304·5
77	59	59	1		
Ethyl propionylmandelate					
*C(C_6H_5)	($CO.OC_2H_5$)	($O.C_3H_5O$)	(H)	−113·7	−268·3
77	73	73	1		

---

[1] Guye has introduced another constant of rotation, besides the specific and molecular rotations, which he terms the molecular deviation, and which is given by the formula

$$[\delta]_D = \frac{\alpha}{l} \cdot \sqrt[3]{\frac{M}{d}},$$

where α is the observed angle of rotation, l the length (in decimetres) of the layer, M the molecular weight, and d the density of the substance. [This deviation is obviously equal to the rotation for unit length multiplied by the cube root of the molecular volume.] Aignau, *C. r.* **120**, 723 (1895), doubts the validity of this formula.

[2] Walden, *Zt. ph. Chem.* **15**, 638 (1894); **17**, 245, 705 (1895).

[3] Walden, *Zt. ph. Chem.* **17**, 245, 712 (1895).

Dimethyl propionylmalate	$[\alpha]_D$	$[M]_D$
$*C(CH_2.CO.OCH_3)\ (CO.OCH_3)\ (O.C_3H_5O)\ (H)$ 73 59 73 1	− 22·9	− 50·0

Dipropyl isovalerylmalate		
$*C(CH_2.CO.OC_3H_7)\ (CO.OC_3H_7)\ (O.C_5H_9O)\ (H)$ 101 87 101 1	− 21·7	− 65·5

2. A change in the order (reversal) of the weights of two groups ought, according to the hypothesis, to give rise to a change in the direction of the rotation, but in many cases no such action occurs. Walden[1] obtained the following results:

Substance	Order of the weights of the groups	Direction of rotation found	Sign of the product of asymmetry
Mandelic acid $*C(C_6H_5)(CO.OH)(OH)(H)$ 77 45 17 1	*a b c d*	+	+
Amyl mandelate $*C(C_6H_5)(CO.OC_5H_{11})(OH)(H)$ . . . 77 115 17 1	*b a c d*	+	−
Acetylmandelic acid $*C(C_6H_5)(CO.OH)(O.C_2H_3O)(H)$ . . . 77 4 5 9 1	*a c b d*	+	−
Dipropyl acetylmalate $*C(CH_2.CO.OC_3H_7)(CO.OC_3H_7)(O.C_2H_3O)(H)$ 101 87 59 1	*a b c d*	+	+
Dipropyl chloracetylmalate $*C(CH_2.CO.OC_3H_7)(CO.OC_3H_7)(O.C_2H_2ClO)(H)$ 101 87 93·5 1	*a c b d*	+	−

---

[1] Walden, *Zt. ph. Chem.* 17, 705 (1895). The compounds were prepared from *l*-mandelic acid, and had therefore the opposite rotation to that given in the table. The same applies to the malic esters.

On the other hand the direction of rotation may change on altering the order of the weights of two groups whilst the product of asymmetry remains of the same sign. For instance:

Substance	Order of the weights of the groups	Direction of rotation found	Sign of the product of asymmetry
Mandelic acid $*C(C_6H_5)(COOH)(OH)(H)$ 77 45 17 1	*a b c d*	+	+
Phenyl-bromacetic acid $*C(C_6H_5)(COOH)(Br)(H)$ 77 45 80 1	*c a b d*	−	+
Phenyl-bromacetyl bromide $*C(C_6H_5)(CO.Br)(Br)(H)$ 77 108 80 1	*b c a d*	−	+
Dimethyl malate $*C(CH_2.CO.OCH_3)(CO.OCH_3)(OH)(H)$ 73 59 17 1 .	*a b c d*	+	+
Dimethyl bromosuccinate $*C(CH_2.CO.OCH_3)(CO.OCH_3)(Br)(H)$ 73 59 80 1 . .	*c a b d*	−	+

3. In homologous series the changes of the rotatory power and of the product of asymmetry do not, in the majority of cases, run parallel, but apparently vary independently of one another.

From these considerations it is evident that the product of asymmetry has not a sufficient basis. As Guye[1] finds, the actions which the four groups attached to the asymmetric carbon atom have on each other is dependent not only on their masses but also on their distance from the carbon atom. The nature of the elements of the four groups has a very great influence on the degree and direction of the rotation. On account of the great complexity of the phenomenon, it will probably not be possible to numerically connect the rotatory power and the atomic structure of the molecule.

---

[1] Guye and Chavanne, *Bull.* [3] 15, 195 (1895); *Arch. phys. nat.* [4] 1, 54 (1896).

[Frankland[1] has recently shown that the coincidence of the maximum rotatory power and maximum product of asymmetry of an homologous series only takes place when the product of asymmetry attains a maximum at or about the propyl or butyl terms. He also suggests that the maximum rotation is dependent on the associated nature of the first few terms of the series leading to abnormal rotations of these initial terms, and not to the existence of a maximum product of asymmetry at all.]

---

[1] Frankland, *J. C. S.* 75, 364 (1899).

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